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Cognition in *t*(1;11) Translocation Carriers and Patients with Psychotic Disorders

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Declaration

I declare that this thesis has been composed solely by myself and that the work presented is my own, except where clearly indicated. As the data for this thesis was collected as part of a wider study – 'The Scottish Family Mental Health Study' - I was responsible for the recruitment of all participants into the study and for arranging appointments for participants to undergo a multi-modal MRI scan, provide a blood sample and undertake a structured clinical interview (see Thomson, Duff et al., 2016). For all participants referred to in this thesis the clinical data was obtained from structured clinical interviews conducted by trained psychiatrists; Professor Douglas Blackwood, Dr Karine MacRitchie and/or Dr Andrew Watson as part of the wider study and I was solely responsible for arranging appointments and collecting all neuropsychological data and self-report questionnaire data. My colleague, Dr Holly Redpath, assisted with the recruitment and data collection of four control participants whose appointments were doubled up for the participants' convenience. The data collected on these occasions were reviewed, discussed and scored by mutual agreement.

I certify that this work has not been submitted for any other degree or professional qualification.

Barbara Jane Duff

19/10/2017

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I would like say a big thank you to all the participants who took part in this study, without whom this work would not have been possible.

I would also like to say a big thank you to my principal supervisor, Professor Stephen Lawrie for his continued professional support, regular deadlines and good humour together with my second supervisor Professor Andrew McIntosh and for their help and guidance throughout this research project. I would also like to extend my thanks to Dr James McKirdy who was initially one of my supervisors.

Data for this thesis was collected as part of a wider study, the Scottish Family Mental Health Study and as such, it involved input from a large number of people. I would therefore like to acknowledge that the results from this study are attributable to a wider team effort. I would like to thank everyone who was involved in the study, in particular Professor Douglas Blackwood from whom I learned a lot and my colleague Holly Redpath who assisted with recruitment and cognitive testing (and outside the study for her continued support, help and humour as a former PhD Student). I would also like to thank Karine MacRitchie, Andrew Watson, Pippa Thomson and Lynsey Hall for their support and technical assistance.

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List of Figures and Tables

Chapter 4

Glossary of Abbreviations

AMS	-	Altman Mania Rating Scale
ANOVA	-	Analysis of Variance
APA	-	American Psychiatric Association
ASRM	-	Altman Self-Rating Mania Rating Scale
BACS	-	Brief Assessment of Cognition in Schizophrenia
BDI	-	Becks Depression Inventory
BPRS	-	Brief Psychiatric Rating Scale
CANTAB	-	Cambridge Neuropsychological Test Automated Battery
CARS-M	-	Clinician-Administered Rating Scale for Mania
CBT	-	Cognitive Behavioural Therapy
CNT	-	Count – (Number of non-missing SNPs used for scoring)
CNV	-	Copy Number Variant
CPT	-	Continuous Performance Task
CPZ	-	Chlorpromazine Equivalent
DISC1	-	Disrupted-in-Schizophrenia 1
DISC2	-	Disrupted-in-Schizophrenia 2
DSM	-	Diagnostic and Statistical Manual
ECT	-	Electroconvulsive Therapy
EPQ	-	Eysenck Personality Questionnaire
ERP	-	Event Related Potential
FDR	-	False Discovery Rate
GAF	-	Global Assessment of Functioning
GAS	-	Global Assessment Scale
GWAS	-	Genome Wide Association Study
HRSD	-	Hamilton Rating Scale for Depression

IQ	-	Intelligence Quotient
KSQ	-	Kings Schizotypy Questionnaire
LBC	-	Lothian Birth Cohort
LC	-	Liability Classes
LSA	-	Latent Semantic Analysis
MDD	-	Major Depressive Disorder
MRC	-	Medical Research Council
MRI	-	Magnetic Resonance Imaging
N	-	Number
NART	-	National Adult Reading Test
NOS	-	No Other Symptoms
OPCRIT	-	Operational Criteria Symptom Checklist
PANSS	-	Positive and Negative Symptoms Scale
PGC	-	Psychiatric Genomics Consortium
PGR	-	Polygenic Risk
PGRBP	-	Polygenic Risk for Bipolar Disorder
PGRMDD	-	Polygenic Risk for Major Depressive Disorder
PGRS	-	Polygenic Risk for Schizophrenia
RTI	-	Reaction Time
SA	-	Schizoaffective
SANS	-	Scale for the Assessment of Negative Symptoms
SCID	-	Structured Clinical Interview for DSM-IV Axis 1 Disorders
SD	-	Standard Deviation
SFMHS	-	Scottish Family Mental Health Study
SNP	-	Single Nucleotide Polymorphism
SPSS	-	Statistical Package for Social Sciences
STG	-	Superior Temporal Gyrus

TEMPS-A	-	Temperament Evaluation of the Memphis, Pisa, Paris and San-Diego-Autoquestionnaire
T/L	-	Translocation
WAIS	-	Wechsler Adult Intelligence Scale
WASI	-	Wechsler Abbreviated Scale of Intelligence
WCST	-	Wisconsin Card Sorting Task
YOUNG	-	Young Mania Rating Scale

Organisation of Thesis

This thesis examines a large multiply affected family with the strongest known genetic risk factor for psychosis, to compare the cognitive profiles in those with and without the risk factor, as well as in those with the risk factor, with and without psychoses. Similar comparisons were made between individuals with schizophrenia and individuals with bipolar disorder as well as a control group of healthy participants. Neuropsychological measures were then related to symptom severity and polygenic risk profile scores. Recruiting individuals with schizophrenia and bipolar disorder also provided a positive control group to enable the comparison of results from the *DISC1 t*(1;11) kindred in addition to establishing any differences between the two conditions.

As direct comparisons between the *DISC1 t*(1;11) kindred and the combined patients group were not warranted due to confounders such as shared heredity and environmental factors, this thesis has been structured in two parts. Firstly to investigate how the cognitive profiles differ between those with and without the known genetic risk factor - *DISC1 t*(1;11) translocation – and how they differ from healthy controls and patients with psychiatric illness (of similar severity) without the genetic risk factor, and secondly to examine how the cognitive profiles differ between those with schizophrenia and bipolar disorder.

Chapter 1 provides a brief overview of the major non-organic psychiatric disorders, i.e. schizophrenia, bipolar disorder and major depressive disorder. This chapter also provides information on diagnosis, epidemiology, course of illness, family and genetics, and cognition. A narrative summary of the neuropsychology of *DISC1* in humans forms Chapter 2 and describes the research findings to date for associations between the *DISC1* gene and measures of cognition.

Findings to date support the current dominant neurodevelopmental hypothesis and question why the *DISC1 t*(1;11) translocation is of interest, what we know so far and what is not there.

The data for this thesis was collected as part of a larger multi-modal imaging study - The Scottish Family Mental Health Study (SFMHS) - which formed the third major follow-up of this unique family. The history and background of the previous two follow up studies, together with details of the original Scottish pedigree are provided in Chapter 1. The SFMH study provided the first opportunity to investigate the rare *DISC1 t*(1;11) translocation with brain structure, function and chemistry, particularly glutamate. My primary role in the SFMH study was to recruit members of the *DISC1 t*(1;11) kindred, together with patients and control participants; arrange for participants to undertake a multi-modal MRI scan, provide a blood sample and undertake a full clinical interview. As the effect (if any) of the rare *DISC1 t*(1;11) translocation on cognition has not been fully investigated, I conducted a full neuropsychological test battery which provided the initial data for this thesis.

As all participants were recruited as part of the wider SFMH study, all five groups (*DISC1 t*(1;11) carriers, *DISC1 t*(1;11) non-carriers, individuals with schizophrenia, individuals with bipolar disorder and healthy control participants) followed the same protocol and procedure, therefore methodology covering recruitment, assessments and procedure, aims, hypotheses and analysis are detailed in one chapter (Chapter 3), however there are two separate results chapters. Chapter 4 provides results for *DISC1 t*(1;11) carriers and non-carriers and Chapter 5 provides results for the patient samples and healthy control participants.

A synthesis summarising the aims and overall results of this thesis, together with suggested directions for future work, limitations of the study and final conclusions are provided in Chapter 6.

Abstract

Deficits in a number of cognitive domains have been associated with core symptoms of schizophrenia, including working memory, attention, motor skills, reaction time, episodic memory and executive function. Bipolar Disorder is also associated with cognitive impairment; however the level of impairment appears to be less severe than that seen in schizophrenia.

A translocation (*t*(1;11)) containing the Disrupted-in-Schizophrenia 1 (*DISC1*) gene has been found to be highly associated with schizophrenia, bipolar disorder and major depressive disorder. As such, this gene has been the focus of much research and to date *DISC1* has been found to be associated with brain development, brain structure and the glutamate system - all key factors in current models of schizophrenia and affective disorders.

The aim of this PhD is to identify cognitive domains that are differentially impaired or unimpaired in a large Scottish family, some of whom carry this rare *DISC1* variant, a balanced translocation (*t* (1;11) (q 42; q14.3)), that segregates with schizophrenia and affective disorders, as well as psychiatric patients with schizophrenia and bipolar disorder and healthy control subjects.

All participants have undergone standardised cognitive assessments to measure premorbid I.Q. (NART), current I.Q. (WASI) verbal memory, working memory, verbal fluency, processing speed, motor skills, executive function (BACS) and selected CANTAB tasks to assess simple and five-choice reaction time. Polygenic risk profile scores and self-report questionnaire data have also been investigated.

Results indicate an impact of the *DISC1 t*(1;11) translocation on general intelligence and attention and processing speed.

Significant differences were also identified between *DISC1 t*(1;11) carriers and non-carriers on self-report questionnaire data. Mean scores for polygenic risk for bipolar disorder were significantly different between *DISC1 t*(1;11) carriers and non-carriers and polygenic risk for schizophrenia was significantly associated with symptom severity, as measured by the Positive and Negative Symptom Scale (PANSS).

Within the patient groups, a measure of processing speed (the token motor task) was found to be significantly different between those with schizophrenia and bipolar disorder and there was also a trend for attention and processing speed. As expected, I.Q. was significantly different between patients and control participants. Clinical ratings were significantly associated with neuropsychological and self-report measures. Polygenic risk for major depressive disorder was found to be significantly associated with impaired general intelligence (current IQ) and slowed reaction time in patients who were not currently depressed, suggesting there may be genetic risk markers in this population which impact on cognition. This is a novel finding and further suggests the possibility of a biological component related to the genetics of depression.

In conclusion, and in line with the literature, psychosis has a negative impact on cognition with reduced performance across several neuropsychological tasks between patient groups, with schizophrenia patients performing worse than patients with bipolar disorder and both patient groups performing worse than healthy control participants. Cognition is markedly more impaired in *DISC1 t*(1;11) translocation carriers and especially in those with psychosis. The *DISC1 t*(1;11) translocation and psychosis may therefore confer a "double hit" on cognition - in addition to psychosis itself - which is known to impair cognitive function, significantly increasing the level of cognitive impairment and increasing the risk for psychosis in general.

Lay Summary

Cognition is essential for making sense of and understanding the world around us. It includes thinking, learning, understanding and remembering. These abilities help people to perform and enjoy their daily routines, develop employment skills, socialise, be motivated to set and achieve goals, enjoy sports and/or other hobbies etc. If these abilities are damaged however, it can often have a devastating impact, and in the case of schizophrenia, and to a lesser extent, bipolar disorder, activities which are taken for granted by most, can become difficult if not impossible. In the most severe cases, it can even determine people's living status, occupation and social abilities. Understanding more about the reasons why cognition becomes impaired in mental illness and being able to improve it would lead to much better outcomes and quality of life for people who suffer from these disorders. It is hoped it would also go some way to addressing important humanitarian and public health concerns.

This thesis has two parts – firstly it investigated cognition in people who have a higher than usual risk of developing a major mental illness due to a big difference in their genetic make-up. This difference is very rare but important to study, as it may tell us more about how problems with thinking and memory differ between people with and without this genetic difference, and about how these problems develop. This thesis also found that the genetic difference does impact on general intelligence and on attention and processing speed, and that this difference points to the problems being developmental in nature. People with the genetic difference were also found to have a higher polygenic risk (lots of genes each with a very small effect, but a much larger effect together) of developing a major mental illness such as schizophrenia, bipolar disorder and/or major depression and this is something that can be investigated in more detail in the future.

The second part of this thesis investigated cognition in people with schizophrenia and people with bipolar disorder, as well as in people who have no history of mental ill-health. This allowed the results from the first group with the genetic difference to be compared with the results from people with a psychiatric illness in general, to find out if there were differences that could be caused by differences in their genetic make-up. It found a difference in motor speed between people with schizophrenia and people with bipolar disorder and a group difference was identified in the people with the genetic risk that wasn't found in the people with psychiatric illness in general, pointing to an effect of their genetic make-up. As before, polygenic risk was again found to be related to a number of cognitive abilities in these groups of people, making it a promising area that can be examined more in the future.

Chapter 1: Introduction

1. Brief Overview of Major Non-Organic Psychiatric Disorders

1.1 Schizophrenia

The name 'schizophrenia' was coined 100 years ago by Eugen Bleuler, originating from the Greek 'schizein' – meaning 'to split' and 'phren', meaning 'mind' (Kuhn, 2004). Bleuler considered the term 'splitting of the mind' to relate to the separation of function between thinking, memory, perception and personality (Bleuler & Bleuler, 1986). Schizophrenia refers to a disease concept generally considered to have been defined by Emil Kraepelin (1856 – 1927) who stated that "*appropriate investigations would eventually reveal the nature of this brain disease*" (Lawrie et al., 2004), and although an exact aetiology has yet to be discovered, advances in medical science and technology are successfully deciphering the complex coding of this irreversible, often extremely disabling major mental illness.

1.1.1 Definition

Schizophrenia usually emerges in late adolescence or early adult life, often striking people down in their prime (Johnstone et al., 2010). The symptomology of schizophrenia is characterised by 'positive' symptoms, 'negative' symptoms and impaired cognitive function. Positive symptoms most commonly consist of auditory and/or visual hallucinations – for example, hearing voices that no-one else can hear, and/or seeing people or objects that are not there.

Hallucinations can involve all of the senses and although not as common, olfactory, tactile and gustatory hallucinations – i.e. smelling odours that others cannot; feeling things that are not there and/or experiencing a bad taste may also be experienced (Johnstone et al., 2010).

Positive symptomology also refers to delusions, i.e. false beliefs, and include paranoia – for example, individuals believing they are being spied on; their conversations are being listened to; and/or they believe people are always talking about them. Most characteristically, delusions involve various passivity phenomena, for example, people report the feeling that they are being controlled or influenced by a mysterious force and/or alien force. Others report thought insertion, thought withdrawal or thought broadcasting. (Johnstone et al., 2010). Hallucinations are typically referred to as the manifestation of psychosis; with individuals often requiring immediate psychiatric help.

Negative symptoms are not as obvious as positive symptoms, which are abnormal by their presence; however negative symptoms are equally disabling and difficult to manage. While positive symptoms can usually be successfully managed by pharmaceutical interventions, the same cannot be said for negative symptoms, resulting in an adverse effect on prognosis and eventual functional outcome. Negative symptoms include social withdrawal, poverty of speech and lack of motivation – symptoms recognised by their absence. Individuals stricken with schizophrenia often transform from previously active, social and independent people into inactive, withdrawn and often completely dependent people. Employment can often become unrealistic for many, as can personal relationships, isolating those affected (Johnstone et al., 2010).

1.1.2 Diagnosis

To meet a diagnosis of schizophrenia in line with the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) (American Psychiatric Association, 2013) individuals will have had the illness for at least six months and have experienced at least two of the following symptoms which should have been present for a prolonged period of time during a one month period - one of which must include either delusions, hallucinations or disorganised speech, together with grossly disorganized or catatonic behaviour and/or negative symptoms (i.e., diminished emotional expression or avolition). These criteria are slightly different to earlier editions which previously required only one of the specified symptoms from Criterion 'A' to be present, however the American Psychiatric Association (APA) who are the publishers of the Diagnostic and Statistical Manual of Mental Disorders, made this change based on the past 15 years of schizophrenia research to better refine the diagnostic criteria for schizophrenia (Grohol, 2014).

1.1.3 Epidemiology

According to the World Health Organisation, (1998) schizophrenia is one of the largest contributors to the global burden of disease, ranking in the top ten illnesses. Schizophrenia has a lifetime risk of around 1% of the population worldwide, affecting more than 21 million people. Prevalence (i.e. the number of cases in a population at any one time point) internationally is approximately 5 in every 1000 and incidence (i.e. the number of new cases annually) is approximately 0.2 in every 1000.

As previously mentioned, age of first onset of psychosis is usually late teens to early adulthood; however females can have a later age of first onset. Schizophrenia affects both males and females; however more males are affected than females.

Although the exact cause(s) of schizophrenia remains unknown, there are a number of genetic and environmental risk factors associated with the development of schizophrenia including heritability and familial risk, obstetric complications, living in an urban area, time of year of birth – significantly winter and early spring, immigration and older paternal age all contributing (World Health Organisation, 1998). Cannabis and other drug use, as well as alcohol, are also believed to play a part in the later development (or prolonged duration) of major mental illness (NHS Choices, 2015).

Schizophrenia has been found to reduce life expectancy by approximately 10 – 25 years (Laursen et al., 2012), as a result of its association with poor lifestyle - for example, obesity, poor diet, smoking and lack of exercise. Suicide rates are also higher than average in schizophrenia (Palmer et al., 2005; Hor et al., 2010). Schizophrenia has a large economic cost as well as a large human cost as it is a major cause of disability – ranked 3rd after paraplegia and blindness (World Health Organisation, 2007) therefore being able to identify new targets for treatment to improve the functional outcome and quality of life for sufferers is priority.

1.1.4 Course of Illness and Treatment

Schizophrenia is most commonly diagnosed after an individual experiences their first psychotic episode, at which point they will usually be seen by a psychiatrist. It's possible however, that up until this point, symptoms may still have been present, although these wouldn't necessarily have met the threshold for a diagnosis of schizophrenia. This phase of illness is known as the prodromal period, in which negative symptoms, including social withdrawal, loss of motivation, flat affect and loss of experiencing pleasure may also have been present (Johnstone et al., 2010).

Prognosis after this point depends a lot on response to treatment and the severity of any cognitive impairment. Chronic schizophrenia can often be successfully managed with medication, and some individuals are able to return to work and live independent and productive lives, however for those who do not respond well to treatment, or who are more severely impaired, the outlook is less favourable. These individuals may require family support and/or help from community housing and/or a support worker visiting daily to assist with personal care, meals and activities. As cognitive function can continue to decline throughout the course of the illness (Johnstone et al., 2010), some individuals could eventually become completely reliant on family and/or community support to assist them with every aspect of their lives.

Positive symptoms of schizophrenia are usually managed successfully by the use of antipsychotic medication. Chlorpromazine was discovered circa 1952 and revolutionised patient care (Turner, 2007). Chlorpromazine is still used today; however there are now an additional number of effective antipsychotics which can be used solely, or in combination with other mood stabilizers and/or antidepressant medications. As the effects of schizophrenia can sometimes be prolonged and incapacitating (Turner, 2007), antipsychotic medication can provide patients with the ability to reconnect with their loved ones and carers, making it hard not to see chlorpromazine (and other antipsychotics) as almost a psychic penicillin (Turner, 2007).

Non-pharmacological interventions such as cognitive behavioural therapy (CBT) and psycho-education are also promising therapeutic treatment options which may be able to offer respite from some of the harder to treat negative symptoms (Cooke, 2014).

1.1.5 Familial and Genetic Factors

Schizophrenia is familial (O'Donovan et al., 2009) and highly heritable (Harrison & Owen, 2003; O'Donovan et al., 2009). Specific genetic markers have been identified in patients with schizophrenia (Sullivan et al., 2003; Kieseppa et al., 2004; Harrison & Weinberger, 2005; Stefansson et al., 2009) and there is also compelling evidence from a number of family, twin and adoption studies which report that genetic factors are important in how schizophrenia is transmitted (Johnstone et al., 1999; Harrison & Weinberger, 2005).

Genetic research of schizophrenia has moved to finer mapping techniques in the search for likely candidate interactors such as single nucleotide polymorphisms (SNPs) which are responsible for transmitting the correct coding instructions during development, while collaborative genome-wide association studies (GWAS) and linkage studies have begun to identify rare mutations, deletions and duplications of genetic structures and translocations. Until now, GWAS had identified around 30 schizophrenia-associated loci, however the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) have recently identified 108 independent schizophrenia-associated genomic loci (Ripke et al., 2014).

As can be seen from Table 1.1 however, this does not explain all of the variance in liability to the illness, therefore environmental factors must also be considered.

Table 1.1

Morbid Risk of Schizophrenia (Definite and Probable) for Relatives of Schizophrenic Patients

Relationship	**% Shared genes**	**Risk (%)**
General population	N.A.	1
Spouses of patients	N.A.	2
Third-degree relatives	12.5	
First cousins		2
Second-degree relatives	25	
Uncles/aunts		2
Nieces/nephews		4
Grandchildren		5
Half-siblings		6
First-degree relatives	50	
Parents		6
Siblings		9
Children		13
Siblings with 1 schizophrenic parent		17
Dizygotic twin		17
Monozygotic twin	100	48
Children with 2 schizophrenic parents	100	46

Adapted with permission from Gottesman 1991.

1.2 Bipolar Affective Disorder

Bipolar affective disorder, previously known as 'manic depressive disorder', is a complex major mental disease. Originally introduced as an illness by Falret in 1851 as '*folie circulaire'*, this translated to 'circular madness' and described manic and melancholic episodes which were separated by symptom-free periods (Angst & Sellaro, 2000). '*Folie à double forme*' was a term used by Baillarger (1854) to describe cyclic episodes (manic-melancholic) and these were also referred to by Kraepelin as 'double attacks'. Mixed states were also known in the early 19th century and were referred to as 'mixtures' by Heinroth (1818) as well as 'middle forms' by Griesinger (1845). Three specific mixed states – 'manic stupor', 'unproductive mania' (elated mood, inhibition of thinking and increased motor activity) and 'agitated melancholia' (depression with flight of ideas and agitation) were defined by Weygandt (1899) and were later used as the basis for Kraepelin's textbook descriptions (1899) (Kraepelin, E. 1971).

By the late 19th century, Kraepelin (1913) had unified mood disorders and, as a result, bipolar disorders were considered to be part of a broad group known as 'manic depressive insanity' (MDI) which incorporated single episodes as well as recurrent depression. As a result of the unification of affective disorders, research studies often failed to distinguish between mania, bipolar disorder and depression (Angst & Sellaro, 2000). The distinction between these disorders (mania, depression and bipolar disorder), however, was disputed by some, and the categories were maintained in several studies including Pilcz (1901) and Ballet (1903) (Angst & Sellaro, 2000).

1.2.1 Definition

Bipolar Affective Disorder is highly recurrent (Angst & Sellaro, 2000) and usually occurs during the later teenage years or during early adulthood and is likely to persist throughout the lifespan (National Institute of Mental Health, 2015). Symptoms of bipolar disorder include periods of mania in which individuals experience feelings of elation.

Mania is usually (but not always) followed by depressive episodes in which individuals experience feelings of intense despair. 'Mixed' episodes can also be experienced in which, for example, individuals may be suffering from a depressive episode but they also have manic feelings of over-activity or restlessness. Mixed episodes are also the most problematic, having a poorer prognosis, higher risk for chronicity and slower remissions (Angst & Sellaro, 2000).

The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) (American Psychiatric Association, 2013) categorises Bipolar Affective Disorder as either: Bipolar 1 Disorder; Bipolar II Disorder; Cyclothymic Disorder; Substance/Medication-Induced Bipolar and Related Disorder; Bipolar and Related Disorder due to another Medical Condition; Other Specified Bipolar and Related Disorder or Unspecified Bipolar and Related Disorder. Bipolar 1 is characterised by at least one manic episode lasting longer than 1 week. Usually, individuals with Bipolar 1 will also experience episodes of depression, although it is possible to have only manic episodes. If the illness is left untreated, manic episodes could last as long as 3 – 6 months and depressive episodes could last as long as 12 months.

Bipolar II is characterised by several episodes of severe depression, however manic episodes are milder. Rapid cycling can occur with both types I and II and is characterised by individuals suffering from more than 4 mood swings in a 12 month period.

Cyclothymic Disorder is characterised by milder mood swings than those experienced with full bipolar disorder, however although milder, they can last longer and can sometimes develop into full bipolar disorder (American Psychiatric Association, 2013).

Mania and depression affect an individual's emotions, thinking, physiology and behaviour. During a manic episode, sufferers can feel ecstatically happy; can have lots of new ideas and also make some bad decisions; go without sleep and feel full of energy; talk and move around very quickly, display odd behaviour, spend money recklessly etc.

During a depressive episode, individuals can feel extreme sadness, the feeling they want to burst into tears for no apparent reason; they struggle to make basic decisions and struggle to see any positives; struggle to sleep, lose their appetite. Individuals could also have difficulty completing basic everyday chores and often avoid others (NHS Choices, 2016).

During very severe periods of mania or depression, individuals can also experience psychotic symptoms, i.e. delusions and/or hallucinations. During mania, delusions are usually in the form of grandiose beliefs about themselves, i.e. that they are special, they are better than everyone else, their ways are best, they know better, etc. Individuals can often also believe they have super powers – for example, they believe they can heal the sick. Psychotic symptoms during a severe period of depression can result in very negative delusions, i.e. individuals can become extremely self-critical, self-blaming and self-punishing and can experience feelings of worthlessness and guilt (Mental Health Care, 2012). People suffering from psychotic depression in bipolar disorder also have a higher risk of suicide, as much as 20 - 30 times that of the general population (Pompili et al, 2013).

Hallucinations could manifest in the form of seeing; hearing; smelling, tasting or feeling something that isn't actually there (Johnstone et al., 2010). In between periods of mania and depression, sufferers were thought to be symptom free; however research has found this isn't strictly the case. Although severe symptoms seem to disappear, studies have discovered that in some cases, mild symptoms actually persist, causing problems with thinking, and the continuation of mild depressive symptoms (Royal College of Psychiatrists, 2015).

1.2.2 Diagnosis

To meet a diagnosis of Bipolar Affective Disorder, the Diagnostic and Statistical Manual 5th Edition (DSM-5) (American Psychiatric Association, 2013) criteria for mania and depression are as follows:

Mania is characterised by:

A. "*A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary*)".

B. During this period, at least 3 from a list of specified symptoms must have persisted (4 if the mood is only irritable) and have been present to a significant degree.

Major Depressive Disorder is characterised by:

"*Depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks*" and at least 5 of 9 specified symptoms that "*cause clinically significant impairment in social, work, or other important areas of functioning almost every day"*.

In addition to the above, diagnosis for a Major Depressive Disorder requires two or more major depressive episodes and the severity of episodes for both mania and depression is rated by the physician using various observational and clinical rating scales (American Psychiatric Association, 2013).

1.2.3 Epidemiology

In the general population, lifetime prevalence rates of bipolar disorder are estimated between 1 - 5% and between 0.5 - 3% for bipolar II. The estimate rises to between 2.8% - 6.5% when the full spectrum of bipolar conditions are considered. Bipolar disorder appears to affect men and women equally, however more women are diagnosed with Bipolar II, and women are more likely to suffer rapid-cycling and mixed states than men. Age of onset is usually late teens or early adulthood, however the timescale between the experience of a first episode and actually receiving treatment can be anywhere between 5 – 10 years (Bauer & Pfennig, 2005).

Suicide is a high risk for bipolar patients with up to 20% dying this way (Pompili et al., 2013). Severity of illness, genetic and familial factors, together with loss of support (medical or social), adverse childhood and/or environmental experiences and psychiatric comorbidity were all factors found by the Stanley Foundation Bipolar Network which contributed to the risk of suicide (Bauer & Pfennig, 2005).

1.2.4 Course of Illness and Treatment

It is likely that affected individuals will have experienced bipolarity symptoms for some time prior to receiving a diagnosis (Bauer & Pfennig, 2005). Studies have found that sufferers can often go untreated for lengthy periods of time, estimated to be between 5 – 10 years after experiencing their first episode (Bauer & Pfennig, 2005).

Symptoms can usually be successfully managed with mood stabilisers; however because bipolar disorder is a lifelong illness, it is also likely that this will be lifelong (National Institute of Mental Health, 2015).

Bipolar disorder develops approximately 10 years earlier than recurrent depression (usually in adolescence) with mania typically manifesting in the early 20's (Angst & Sellaro, 2000).

Studies have found that over the lifetime, females with bipolar disorder experience more depressive episodes than men, and the proportion of depressive and manic episodes remains stable (Angst & Sellaro, 2000). There is a higher risk of chronicity with mixed episodes in which remissions are also slower (Bauer & Pfennig, 2005).

The mean length of episodes has been reported to be between 3 and 6 months in clinical studies, however this reduces to between 2 to 3 months in epidemiological studies. Bipolar disorder is relentless in its recurrence and during its course, affective episodes continue throughout the lifespan in an irregular pattern. As previously stated, during periods of remission which were essentially believed to be symptom-free, it is now known that sufferers often continue to experience residual hypomanic or depressive symptoms and continued functional impairment. Overall, bipolar disorder has a poor prognosis as a result of its high recurrence, chronicity of episodes, residual depressive or hypomanic symptoms and early death due to suicide (Angst & Sellaro, 2000).

Antidepressant medication is an effective treatment; however those who respond well to antidepressants may still require maintenance treatment during affective episodes (Angst & Sellaro, 2000). Maintenance treatments usually require a mood stabiliser, for example lithium, and in the case of psychosis, antipsychotic medication may also be required.

Psycho-education is also an effective tool for prevention as it teaches sufferers how to recognise the early signs that they may be about to experience another affective episode. Psychological therapies, for example, cognitive behavioural therapy (CBT) is also helpful in the management of bipolar spectrum disorders (Lam et al., 2000). Individuals with Bipolar disorder are often able to continue to work and live independently in the community, maintain relationships and lead very successful productive lives; however for those whose episodes are more severe, family and/or community support may be required in addition to periods of hospitalisation (Mind, 2015).

1.2.5 Familial and Genetic Factors

From a familial and genetic view, bipolar disorder is one of the most extensively studied psychiatric disorders (Smoller & Finn, 2003). There is a consistent body of evidence from family, twin and adoption studies which supports the existence of genes which predispose people to the risk of developing bipolar disorder. As the level of relatedness to an individual with bipolar disorder diminishes, so does the level of risk a related family member has of developing a mood disorder (Craddock et al., 2005). Heritability estimates are high, with one study reporting 89% in a UK twin pairs study (McGuffin et al., 2003) and 93% in a Finnish study of same-sex twin pairs (Kieseppa et al., 2004).

Although not as well studied as schizophrenia, there is growing evidence that consistently highlights specific genetic regions which are believed to be involved in the pathophysiology of bipolar disorder (Craddock et al., 2005). Recent association studies have identified specific genes, significantly *CACNA1C* and *ANK3* which provide strong evidence for association with bipolar disorder (Ferreira et al., 2008; Sklar et al., 2011).

Sklar et al., (2011) have also identified a new variant in *ODZ4* which also achieved genome-wide significance for association with bipolar disorder. These recent findings highlight the importance of using large samples to identify the genetic architecture of major mental illnesses.

1.3 Major Depressive Disorder

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders seen in primary care (Sharp et al., 2002) and was originally described by Hippocrates as a distinct disease which had both physical and mental symptoms (Hippocrates, Aphorisms, Section: 6.23). During the 17th to 19th centuries, the term 'depression' from the Latin verb '*deprimere'*, meaning 'to press down' (McMullen & Conway, 2002) was introduced.

Symptoms of depression have been described as far back as classical times, resulting in numerous theories including humoral theory, i.e. the four humours (black bile, yellow bile, blood and phlegm) (US National Library of Medicine, 2012), moral and spiritual theories, for example 'acedia' (absence of caring or sloth) (Daly, 2007) and depression was also likened to mourning by Freud (Carhart-Harris et al., 2008). Mixed social and biological theories have been proposed (Lewis, 1934), as well as theories from cognitive psychologists such as Aaron Beck who proposed that depression was caused by a 'cognitive triad' (Beck, 1979). Psychodynamic theories - i.e. existential and humanistic - were also offered (Freeman et al., 1986), and by the mid twentieth century, researchers had proposed that depression was caused by a chemical imbalance in neurotransmitters in the brain (Schildkraut, 1965). In the mid 1970's, as part of proposals for diagnostic criteria based on patterns of symptoms, the term 'Major Depressive Disorder' was introduced by US clinicians (Spitzer et al., 1975), and was incorporated into the Diagnostic and Statistical Manual, 3rd edition in 1980 (DSM-III) (American Psychiatric Association, 1980).

DSM-III diagnostic thresholds included mild depressive episodes, with higher categories for moderate to severe episodes (Gruenberg et al., 2005).

As very severe episodes of depression could result in psychotic features, DSM-IV (American Psychiatric Association, 2000) classified psychotic major depression as a subtype or variant of major depressive disorder (Park et al., 2014). Psychotic major depression denotes the presence of psychotic symptoms, such as delusions and hallucinations as well as the depressive disorder (Park et al., 2014).

1.3.1 Definition

As the term 'depression' literally means 'to press down', it was introduced as a means of describing the change in a person's emotions and affect, as if these were being pressed down (McMullen & Conway, 2002). Depression is a mood disorder and its symptoms are complex and vary widely from person to person. Symptoms range from mild to very severe and can happen once in a lifetime, known as a single episode, or symptoms can recur throughout the lifetime, known as recurrent episodes (World Health Organisation, 2012). Previously well individuals often begin to find themselves crying for no apparent reason, having persistent low mood and feeling great sadness. Symptoms also include the person losing interest and/or pleasure in activities they previously used to enjoy, losing motivation, feelings of guilt, talking and/or moving slower, unexplained aches and pains and having suicidal thoughts (NHS Choices, 2014). Depression can also affect work and family life, and symptoms can last from a few weeks or months to years. Depression affects people psychologically, physically and socially, depending on the severity and duration of the symptoms being experienced (World Health Organisation, 2012).

A mild episode will have some impact on a person's daily life, a moderate episode will have a significant impact on daily life and a severe episode will result in the person finding it almost impossible to manage their daily routines.

Severe depression can also result in the person experiencing psychotic symptoms which will almost certainly require the individual to be hospitalised for treatment (Mental Health Care, 2012).

Depression is often mistaken for grief, which does have similar symptoms, however if a person is suffering from grief - which is a natural response to loss (usually of a loved one) – their sadness will come and go, rather than be continual, and they will still usually be able to enjoy certain things and be able to look forward to the future. If a person is suffering from depression however - which is an illness – their low mood will be continual and they will not be able to enjoy anything or be able to look forward to the future (NHS Choices, 2014).

1.3.2 Diagnosis

To meet a diagnosis of a major depressive episode, an individual will have experienced at least five core criterion symptoms from Criterion 'A', one of which will be either depressed mood or loss of pleasure/interest for a period of at least two weeks - representing a change in the individuals' usual functioning. In addition, the symptoms will have caused clinically significant impairment or distress in their occupational, social or other important areas of functioning e.g. family life, hobbies, etc. (Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), (American Psychiatric Association, 2013).

For recurrent major depression, the individual will have experienced two or more episodes separated by a period of at least two months, during which their symptoms do not meet criteria to be classed as a major depressive episode. Severity of symptoms will determine the classification, i.e. whether the episode is mild, moderate or severe.

Severe episodes will be further determined by the presence or absence of psychotic symptoms (American Psychiatric Association, 2013).

Psychotic major depression is the most severe with sufferers experiencing delusions and/or hallucinations, most commonly auditory and/or visual, in addition to the depressive episode itself (American Psychiatric Association, 2013). Critically, the content of these delusions/hallucinations is mood congruent, i.e. negative.

1.3.3 Epidemiology

According to the World Health Organisation in October 2012, depression was stated as a leading cause of disability worldwide, globally affecting over 350 million people of all ages (World Health Organisation, 2016). There are many potential risk factors for the development of depression, for example, stressful life events such as the loss of a loved one, divorce, drugs, alcohol, redundancy, head injury, ageing and money problems. These can be single events or a combination of events that together could trigger the onset of a major depressive episode. Certain personality traits such as being very critical of oneself or having low self-esteem are also associated with depression. Having a family history of depression, i.e. a parent, brother or sister who has/has had the illness is also likely to increase a persons' risk of developing depression (NHS Choices, 2014). Lifetime prevalence rates vary per country, with Japan reported as being 3% and the U.S. being 19% (Andrade et al., 2003).

Depression can occur at any age, from childhood to old age, and depression has been found to affect twice as many women than men. At its' worst, depression is responsible for an estimated 800,000 suicides every year (World Health Organisation, 2016).

Although depression can strike at any age, population studies have found that major depression usually has a later age of onset than most other major mental illnesses which typically begin during adolescence – early adulthood. Population studies also reported that individuals suffering from major depression were most likely to experience their first episode in their early twenties, with an estimated peak risk period for onset between mid - late adolescence and the mid-forties (Kessler & Bromet, 2013).

Available data for the U.K. in 2009 reported age of onset for a major depressive episode to be between the ages of 25 – 44 with a second smaller incidence between the ages of 45 – 64 (Rait et al., 2009). More recently, the British Psychological Society published findings from the Office for National Statistics which surveyed 40,000 households and found the highest incidence of mild mental illness occurred in those aged 50 – 54 years. In those aged 16 or over, 19% reported symptoms, and there were higher incidences (27%) in those who were separated or divorced (British Psychological Society, 2013) which is in line with findings from population studies (Kessler & Bromet, 2013). Socioeconomic status and level of education have also been found to be associated with depression and depression is more likely to occur in urban rather than rural areas (Paykel et al., 2003).

1.3.4 Course of Illness and Treatment

Depression develops gradually which makes it more difficult for sufferers to realise that they are actually ill – very often people will try their best to continue with their daily lives and routines as normal, and sometimes the change in them will be noticed and pointed out by a family member, friend or work colleague (NHS Choices, 2014).

Individuals may experience feelings of anxiousness before the onset of a depressive episode as panic and generalized anxiety disorder were found to be strong predictors for secondary major depressive episodes (Hirschfeld et al., 2001). Some of the psychological core criterion symptoms that will likely be experienced include persistent low mood, loss of pleasure and/or loss of interest in activities that used to be enjoyed, lack of concentration, inability to make decisions, hopelessness, feeling worthless, feelings of guilt, irritability, intolerance and thoughts of self-harming or suicide. Physical symptoms include slower speech and/or slower movements, disturbed sleep, fatigue, unexplained aches and pains, weight loss when not dieting or weight gain due to loss or increase of appetite. Socially, sufferers often will often struggle with employment, withdraw from hobbies and events and generally become isolated. Very severe cases can result in psychosis with delusions and/or hallucinations.

Typically, these might be delusions of guilt, sin or nihilism, and any auditory or visual hallucinations are usually critical and/or negative in tone. Individuals will not usually experience all of the above symptoms, however at least five will result in a diagnosis of a major depressive episode (American Psychiatric Association, 2013).

Symptoms can last a few weeks to a few months but can last a lot longer (Kessler & Bromet, 2013). A single episode will see the individual recovering with no further episodes, however for some people, symptoms will return after a period of at least two months during which time their symptoms did not meet the core criterion. A number of people suffer from chronic-recurring major depression, i.e. lasting longer than 1 - 2 years (American Psychiatric Association, 2013).

Depression is treatable pharmacologically and non-pharmacologically with moderate to severe cases treated by the use of anti-depressant (and if necessary, anti-psychotic) medication(s) and talking therapies such as cognitive behavioural therapy (CBT). For very severe cases, including psychotic major depression, ECT (electroconvulsive therapy) is also an effective option, in combination with psychotherapy, anti-depressant and anti-psychotic medications (American Psychiatric Association, 2013). Anti-depressants are not recommended as a first line of treatment for cases of mild depression and the preferred initial treatment is psychosocial which could include self-help groups, self-help books and/or exercise which has been found to be effective in relieving the symptoms of mild depressive episodes (NHS Choices, 2014). Treatments are usually very effective; however chronic-recurrent cases and those with psychotic major depression usually require a maintenance therapy i.e. constantly monitored by way of follow-up appointments (Diagnostic and Statistical Manual for Mental Disorders-5 (DSM-5), American Psychiatric Association, 2013; NHS Choices, 2014).

1.3.5 Familial and Genetic Factors

Family and genetic research of major depression have provided good evidence that this disorder is highly heritable (Whalley et al., 2013). Twin and adoption studies are a classic means of distinguishing between genetic and environmental factors in families where there are a larger number of members affected by illness than would be expected by chance (McGuffin & Katz, 1989).

From early twin studies, genetic factors were found to play an important role, with concordance rates found to be two to five times higher in monozygotic twins compared to dizygotic twins (McGuffin & Katz, 1989). Although heritability plays a part, the genetic architecture of depression remains complex and not fully understood (Thomson et al., 2014).

Association studies have reported that genetic susceptibility to major depression overlaps with that for both bipolar disorder and schizophrenia (Schosser et al., 2010) and to date, no single gene has been identified which can be said to be causal in the development of depression (Nestler et al., 2002; Lewis et al., 2010) although the unique *DISC1 t*(1;11) translocation has shown genome-wide significant linkage for recurrent major depressive disorder (Thomson et al., 2014). Major depression is familial - with heritability estimated to be 0.37 (Wray et al., 2012), however, evidence suggests it is not caused by genetics alone but more likely by a combination of genetic and environmental influences (Sullivan et al., 2000).

Childhood maltreatment (physical and/or emotional) is one of the strongest risk factors for the later development of major mental illness including recurrent major depressive disorder and importantly, psychotic major depression (Holshausen et al., 2014). Other potential environmental risk factors include stress, viral infections, anxiety, drugs and/or alcohol use (Nestler et al., 2002) as well as chronic strains with family relationships and less support networks/social resources (Billings et al., 1983).

1.4 Putative Role of Cognition in Major Non-Organic Psychiatric Disorders

1.4.1. Schizophrenia

Cognitive impairment precedes the onset of schizophrenia (Aylward et al., 1984; Woodberry et al., 2008) however having a lower I.Q. by no means guarantees that an individual will go on to develop a severe mental illness in later life. The issues around impaired cognition as a symptom of schizophrenia are still being debated, however it is recognised that schizophrenia has a negative impact on cognitive function, especially general intelligence (I.Q.), memory and executive function (Heinrichs et al., 1998; Johnstone et al., 1999).

Individuals with schizophrenia demonstrate global intellectual impairments pre-dating psychosis onset. Studies have reported significantly poorer performances in general intelligence in people who have later developed schizophrenia as far back as primary school (Caspi et al., 2003; Osler et al., 2007) with children who later developed schizophrenia performing worse in school tests and/or IQ tests than their healthy peers (Joyce, 2013). Information processing speed is also of importance as it is known to account for 25% of the variance in the general ability of healthy populations (Joyce, 2013). As evidenced from replicated studies that underperformance is evident as far back as childhood, Khan & Keefe, (2013) postulate the possibility that this impairment is present at birth. It is equally possible, however, that impairment occurs at some point during development, but prior to the onset of psychosis, and this lag in brain development may be a crucial early manifestation of the illness (Khan & Keefe, 2013).

Importantly, family studies have revealed neurocognitive deficits in the unaffected relatives of individuals with schizophrenia who performed significantly poorer than healthy control subjects in tests of general intelligence, memory and psychomotor performance (McIntosh et al., 2005) executive functions and attention (Snitz et al., 2006).

Family studies have also shown that symptoms and cognition are dissociable domains which follow different developmental paths, and in doing so they point to impaired cognition as a risk factor for the later development of schizophrenia (Gold, 2004). Following this, genetic model fitting was applied in a twin study which reported that genetic influences substantially contributed to all cognitive domains tested, with the highest heritability found for general intelligence and working memory (Toulopoulou et al., 2007). Recently, cognitive ability was reported as being a true endophenotype for susceptibility to schizophrenia by Lencz et al., (2014) who provided empirical evidence at a molecular level of genetic overlap between cognitive ability and schizophrenia.

Using polygenic risk profiling, McIntosh et al., (2013) also reported association between schizophrenia and cognitive ability. In particular, they reported that an increased polygenic risk of schizophrenia was associated with reduced cognitive ability at age 70 and further, that greater relative decline in cognitive function was also associated with greater polygenic risk for schizophrenia between ages 11 and 70.

1.4.2 Bipolar Disorder

Impaired cognition in bipolar disorder is recognised as a core feature of the illness; however the level of impairment is not as severe or as permanent as that seen in schizophrenia (Bora et al., 2009; Barch & Sheffield, 2014). General intelligence appears to remain intact; however impairment is evident in areas of memory, executive function and processing speed (Lewandowski et al., 2011). It was generally believed that impaired cognition could often return to premorbid levels during euthymic periods, however as previously mentioned elsewhere, evidence suggests that even during periods of euthymia, sufferers continue to experience residual symptoms of hypomania and/or depression (Angst & Sellaro, 2000).

There is also converging evidence of persistent cognitive impairment during euthymic periods which may, in part, be caused by these residual symptoms. Kurtz & Gerraty (2009) found that cognitive impairment persisted in individuals with bipolar disorder during all phases of the illness (euthymic, manic or mixed and depressed episodes) and similar results were reported by Bora et al., (2010) who conducted a meta-analysis of cognitive impairment in affective psychoses and also found cognitive dysfunction in remitted bipolar patients. These findings were supported by Thompson et al., (2005) who studied a large group of verified euthymic bipolar patients and revealed deficits across a broad range of cognitive domains.

In addition to the negative impact on cognition evidenced in individuals with bipolar disorder, research has also identified neuropsychological dysfunction in the unaffected relatives of patients with bipolar disorder resulting in areas of executive control and declarative memory postulated as potential endophenotype markers (Nicol Ferrier et al., 2004; McIntosh et al., 2005).

A meta-analysis of neuropsychological deficits in euthymic bipolar patients identified impaired response inhibition as the most prominent potential cognitive endophenotype for bipolar disorder which was impaired in both euthymic bipolar patients and their unaffected relatives. This study also identified set-shifting ability and verbal memory as further potential cognitive endophenotypes for bipolar disorder (Bora et al., 2009).

Cognition appears to remain intact in bipolar disorder, at least until the experience of a first episode, which differs from schizophrenia, in which cognitive deficits are present prior to illness onset (Lewandowski et al., 2011).

Impairment can deteriorate further, depending on length of illness and severity of episodes, and cognitive ability is most impaired in individuals who experience psychosis (Glahn et al., 2007). Effect of medication may impact on cognitive ability, however cognitive impairment has also been found in drug-free patients (Lewandowski et al., 2011).

1.4.3 Major Depressive Disorder

Cognitive function in major depressive disorder and psychotic major depression has not been studied to the same extent as other major mental illness such as schizophrenia and bipolar disorder (Fleming et al., 2004). However as cognitive function is known to be a critical determinant of outcome, both in everyday functioning and quality of life (Barch & Sheffield, 2014), there is now accumulating evidence that major depression is also accompanied by neuropsychological deficits (Basso, 1999; Baune et al., 2010; Lee et al., 2012). Although cognitive impairment is worse in schizophrenia compared to bipolar disorder and psychotic major depression; the profile of impairment in major depressive disorder has been found to be similar, which is consistent with the idea that this may reflect common neural mechanisms (Barch & Sheffield, 2014).

Studies of patients with psychotic major depression have reported significant impairments in verbal and visual memory, as well as executive functions, attention and language functions (Reichenberg et al., 2009). Cognitive deficits are also a feature of non-psychotic major depression, albeit less severe than those experienced with psychosis (Fleming et al., 2004). A recent longitudinal study reported that in clinical remission, unipolar depressed patients showed deficits in visual memory and processing speed and suggested that executive dysfunction may be a trait marker (Xu et al. 2012).

Genetic studies of cognition for major depression have not as yet identified specific risk genes, however, Thomson et al., (2014) identified *DISC1* putative functional variants that were nominally associated with recurrent major depressive disorder and cognition at the locus wide level of significance, a finding which requires further study.

1.5 History and Background of the *DISC1 t*(1;11) Kindred

The *t*(1;11) translocation was first identified in 1970 in a large Scottish family by Jacobs et al., (1970), however it took some 30 years before the *DISC1* gene was identified and provisionally christened *Disrupted-in-Schizophrenia 1* (Miller et al., 2000), a title which has remained, and which is now commonplace worldwide. The *DISC1* gene, located on chromosome 1q42, together with its' novel counterpart *DISC2*, were so called as a result of much cytogenetic research, resulting in the discovery that gene function was directly disrupted by the *DISC1* gene. It was further hypothesized to be a causative event in the development of schizophrenia and other psychiatric disorders such as bipolar disorder and major depressive disorder (Miller et al., 2000).

The origins of *DISC1* trace back to a large Scottish pedigree with an unusually high number of cases covering a range of psychiatric disorders including schizophrenia, bipolar disorder and major depressive disorder. During a cytogenetic survey of juvenile delinquent boys awaiting admission to a Scottish borstal in 1968, the proband was found to have a balanced translocation between chromosome 1 and a chromosome in group 'C' - later identified as chromosome 11 (1;11)(q42.1;q14.3) (St. Clair et al., 1990).

Jacobs et al., (1970) were able to pinpoint the proband after examining clinical data held by the MRC Cytogenetics Registry in Edinburgh on 282 pedigrees with familial autosomal anomalies (St. Clair et al., 1990). To identify the presence of associated psychiatric illness, each of the 282 pedigrees were examined, and although several isolated associations were found, the proband was the only case of mental ill health within a single pedigree which co-segregated with a chromosomal anomaly (St Clair et al., 1990).

After further investigation, the abnormality was traced through several branches of the family and found to be present in four generations. Additionally, cumulative data gathered by general practitioners from annual follow-ups revealed that many of the other family members had been referred to psychiatrists and/or admitted to psychiatric hospitals during the intervening years (St. Clair et al., 1990).

Around the same time, another family had been identified as having major mental illness co-segregating with a balanced translocation around the same region on chromosome 11 (Smith et al., 1989). The reciprocal breakpoint in this family, however, was found to be at chromosome 9. In view of these findings, it was hypothesized that chromosome 11 (in particular, the region q21-22) warranted further examination in the search for genes that could potentially predispose people to psychiatric illness (St. Clair et al., 1990).

1.5.1 Clinical Phenotypes

From the original cytogenetic study by Jacobs et al., (1970) (Figure 1) no abnormal phenotypes were reported. The family were subsequently followed up by St. Clair et al., (1990) who were able to clinically assess 77 family members (58 living and 19 deceased) (Figure 2). The follow up study was conducted as a result of the additional information from GPs who had continued to provide updates to the MRC Cytogenetics Registry, Edinburgh and reported that a high number of the original family had been admitted to mental hospitals and/or referred to psychiatric services. In total, 34 family members were found to carry the *t(*1;11) translocation and from these, 23 individuals were diagnosed with a psychiatric illness. Eleven individuals had a major mental illness – either schizophrenia, schizoaffective disorder or major depressive disorder (recurrent unipolar) - 2 had died as a result of suicide, 5 had a minor psychiatric illness – either generalised anxiety disorder, minor depressive disorder or alcoholism and a further 5 were receiving specialist treatment for adolescent psychiatric disorders.

From the 43 non-carriers, 5 family members had a psychiatric diagnosis, none of which was a major mental illness (generalised anxiety disorder, minor depressive disorder, alcoholism) (St. Claire et al., 1990).

A further follow-up study was carried out with this family in 2000 by Blackwood et al., (2001) who were able to include 87 family members for karyotype analysis. They also clinically assessed a total of 69 individuals and reported nine new cases of psychiatric illness which had occurred during the previous 10 years. Thirty-seven individuals were found to carry the balanced translocation from which 29 family members received a psychiatric diagnosis. Illnesses included schizophrenia (N=7), bipolar disorder (N=1), major depressive disorder (recurrent) (N=10), adolescent conduct disorder (N=2) and major depressive disorder (single episode) (N=1). Thirty-eight non-carriers were karyotyped from which 5 individuals received a minor diagnosis of either adolescent conduct-and-emotional disorder (N=1), single episode depression (N=3) or alcoholism (N=1) (Figure 3).

The study by Blackwood et al., (2001) was the first to examine cognition and intelligence quotient (I.Q.) in a sub-group of these family members and reported that premorbid I.Q. (measured by the NART) was within the normal range. Further, no difference was found in mean I.Q. scores between translocation carriers and non-carriers. P300 Event Related Potential (ERP) was also recorded in family members (carriers and non-carriers) as well as a group of patients with schizophrenia and a group of healthy control participants. P300 was found to be abnormal in family members – translocation carriers had significantly reduced P300 amplitude compared to non-carriers and further, it became evident that changes in P300 were not exclusive to those individuals with a psychiatric diagnosis.

These are interesting results as changes in P300 amplitude and latency are believed to indicate deficits in short-term memory required for the speed and efficient processing of information and are also considered to be trait markers of risk for the later development of major mental illness.

The *t*(1;11) family remains unique, as to date the *t*(1;11) translocation has not been found in any other individual or family, and their continued willingness to participate in a longitudinal study of this nature affords us the opportunity to conduct further investigations and make use of new technologies that were either not available or as advanced as they are today. Additional investigations may shed more light on the *DISC1* gene itself and further, being able to identify phenotypes that are differentially impaired or unimpaired between translocation carriers and non-carriers may reveal effects directly attributable to the balanced translocation itself.

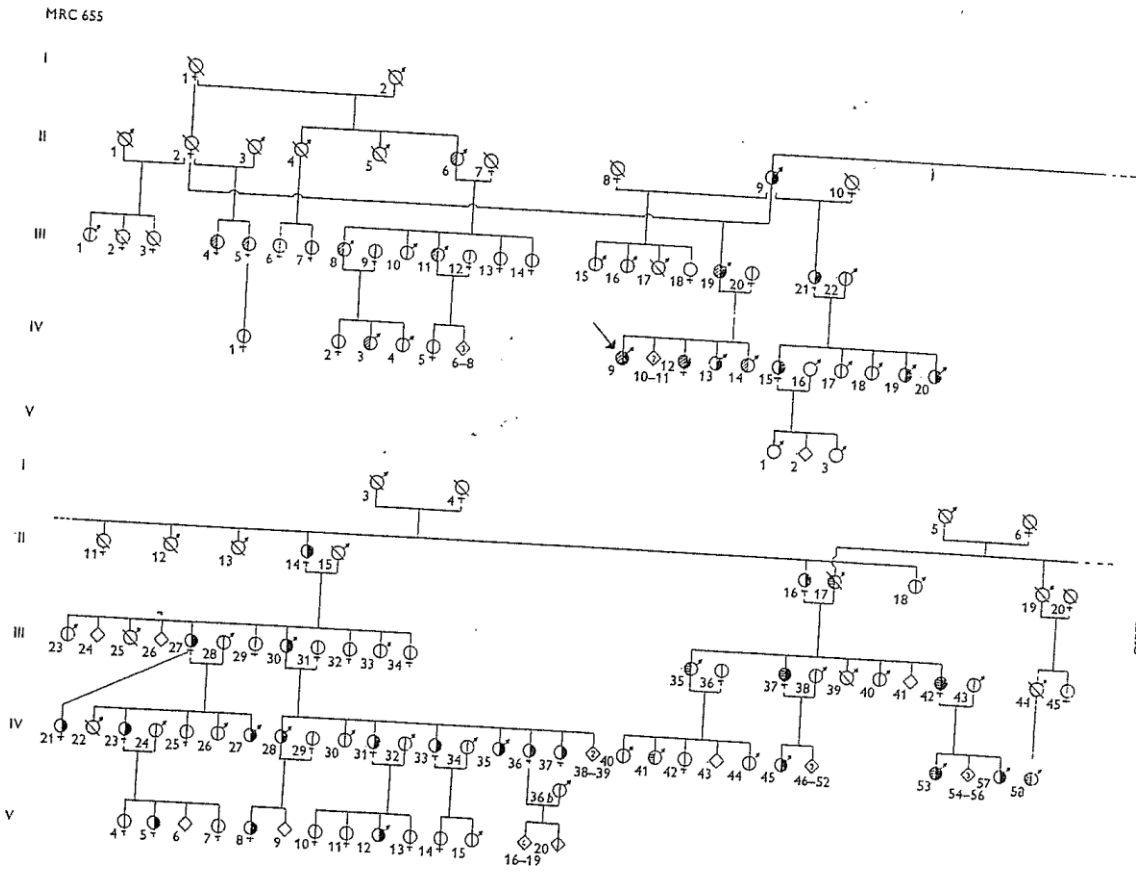
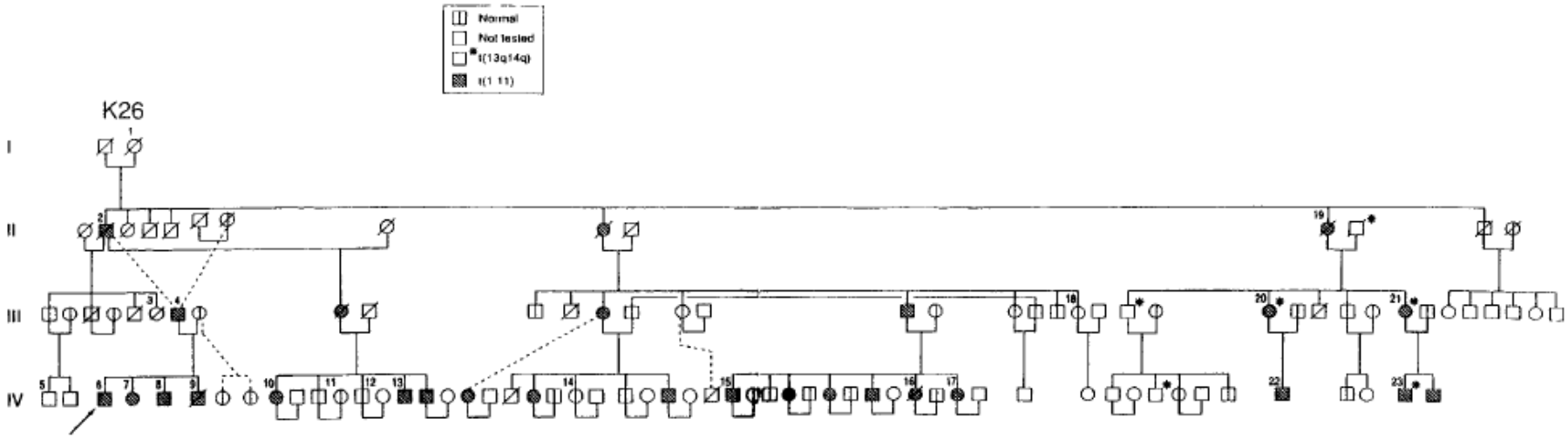


Figure 1.1: Original pedigree, reported as part of a cytogenetic study by Jacobs et al., 1970



Generations I-IV of pedigree K26.

28 of 34 carriers and 27 of 43 non-carriers are shown: the others are in generation V (aged 10–28 years) which is not shown. The 23 documented cases of psychiatric disorders were all in generations I–IV (labelled 1–23).

1: recurrent major depression; attempted suicide; died in mental hospital. 2: recurrent major depression; attempted suicide; died in mental hospital. 3: recurrent major depression, schizoid features; suicide 4: recurrent major depression; attempted suicide. 5: alcoholism 6: severe adolescent conduct disorder, undifferentiated type. 7: severe adolescent conduct disorder and emotional disturbance 8: generalised anxiety disorder; severe emotional disturbance in adolescence. 9: severe adolescent conduct disorder and emotional disturbance. 10: schizophrenia. 11: alcoholism. 12: alcoholism. 13: schizophrenia. 14: minor depressive disorder; single episode only. 15: generalised anxiety disorder. 16: schizoaffective disorder; suicide. 17 recurrent major depression, severe adolescent conduct and emotional disorder, bizarre obsessions and rituals. 18. generalised anxiety and agoraphobia. 19: recurrent major depression. 20: schizophrenia. 21: schizoaffective disorder 22: recurrent major depression. 23: severe schizotypal personality disorder; attended special school for educationally disturbed; long history of bizarre and incongruous behaviour.

Figure 1.2: Family members followed up - from St. Clair et al., 1990.

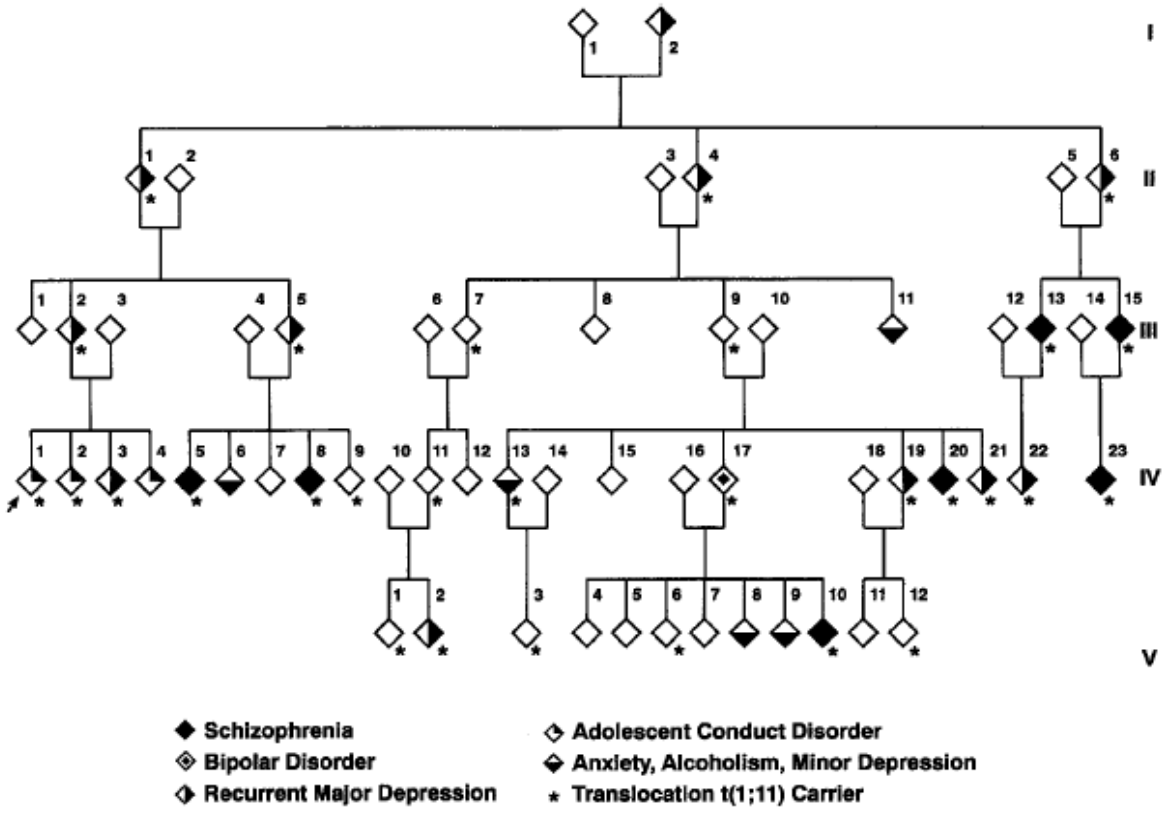


Figure 1.3: Family followed up in 2000 – from Blackwood et al., 2001

1.6 The *DISC1* *t*(1;11) Translocation Phenomenon

The *DISC1* gene is one of the strongest known risk factors for psychosis; however the effect(s) of the *t*(1;11) balanced translocation (Figure 1.4), if any, is not fully understood. To date, cognitive findings specific to the *t*(1;11) translocation are limited and do not appear to suggest any direct impact of the translocation (Blackwood et al., 2001).

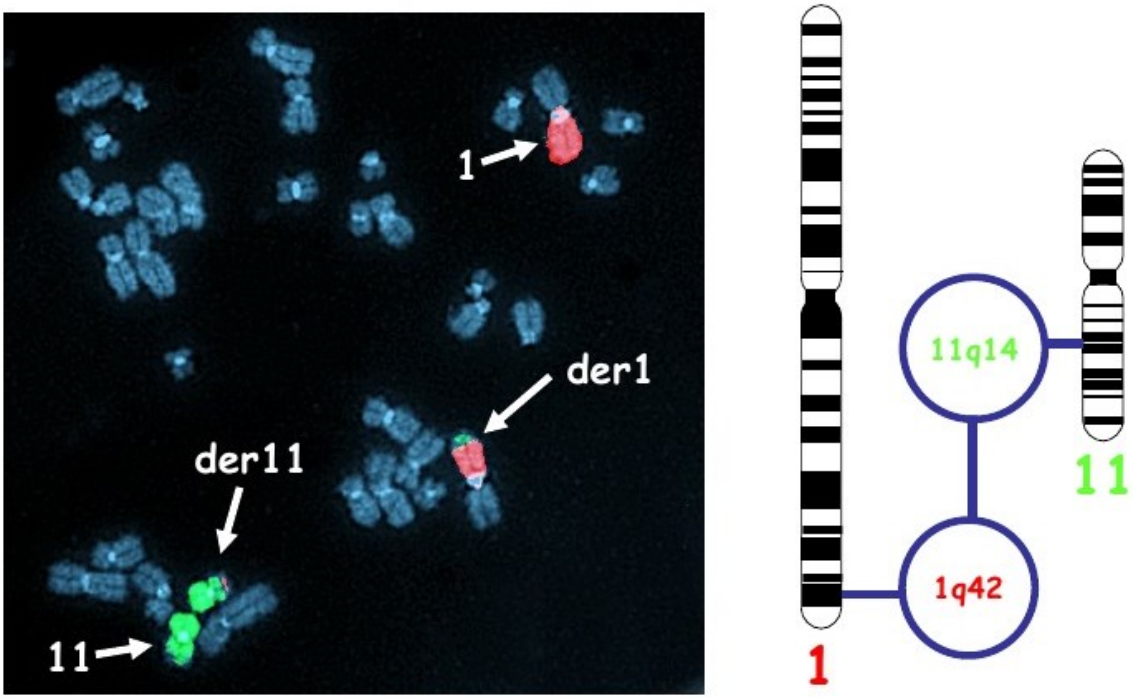


Figure 1.4 *DISC1* *t*(1;11) Balanced Translocation

DISC1 itself is known to be associated with brain development, brain structure and the glutamate system - all key factors in current models of schizophrenia and affective disorders (Harrison & Weinberger, 2005; Chubb et al., 2008).

Studies investigating neurocognitive function and either *DISC1* or the 1q42 region, have reported significant findings across a range of cognitive domains (Gasperoni et al., 2003; Paunio et al., 2004; Burdick et al., 2005; Hennah et al., 2005; Cannon et al., 2005; Thomson et al., 2005; Liu et al., 2006; Palo et al., 2007) (Chapter 2).

Several human neuroimaging studies have also made use of a variety of genetic imaging techniques to investigate *DISC1* together with brain structure and function (see Duff et al., 2013 for a full review).

The breakpoint of the *DISC1* translocation lies within the *DISC1* and *DISC1FP1*/Boymaw genes. Recent work discovered that the breakpoint on chromosome 11 contains biologically relevant DNA (Zhou et al., 2008) and was named both *DISC1* fusion partner 1 (*DISC1FP1*) and Boymaw (Zhou et al., 2008; Eykelenboom et al., 2012).

The *DISC1 t*(1;11) balanced translocation has recently been investigated using a variety of imaging modalities which found that *DISC1* translocation carriers have reduced cortical thickness correlating with positive symptom severity and general psychopathology as well as reduced gyrification in the prefrontal cortex which also correlated with the severity of general psychopathology. Glutamate concentrations in the right dorsolateral prefontal cortex were also found to be significantly reduced (Thomson, Duff et al., 2016). A multi-functional scaffold protein known to mediate several processes implicated in major psychiatric disorders is encoded by *DISC1,* and *DISC1* has also been shown to influence brain function and neurodevelopment in rodent models, in which behaviours believed to model depression and schizophrenia were also found (Thomson, Duff et al., 2016). In a study of *DISC1* transgenic mice, Shen et al., (2008) reported that alterations in the *DISC1* gene lead to reduced neurite outgrowth and the failure of normal neuronal proliferation which lead to large ventricles, reduced cortical size and behavioural changes similar to schizophrenia-like phenotypes.

DISC1 has unexpectedly been linked with Alzheimer's disease by way of a previously unrecognised interaction between APP (Amyloid Precursor Protein) and *DISC1* (Young-Pearse et al., 2010; Shahani et al., 2015; Tomoda et al., 2017).

Although schizophrenia and Alzheimer's disease are clinically distinct conditions, they both result in cognitive impairment and deficits in information processing. As such, future work investigating the molecular aspects of the *DISC1*-APP interaction may provide more clues and improve our understanding of cognitive processes in neurodegenerative disorders (Young-Pearse et al., 2010; Shahani et al., 2015: Tomoda et al., 2017).

Very recent work by Teng et al., (2016) reported that low cognitive ability was associated with rare disruptive variants in the *DISC1* Interactome (a large set of proteins that interact with the *DISC1* protein) and also very recently, supporting the earlier P300 ERP work by Blackwood et al., (2001) a SNP-based analysis identified significant associations between startle latency and two *DISC1* loci, although these did not survive multiple corrections (Smith et al., 2017).

1.6.1 Polygenic Risk Profiling

The *DISC1* locus has been reported as being involved in a broad range of disorders including schizophrenia, schizoaffective disorder, bipolar disorder, recurrent major depression and most recently, in autism spectrum disorders. These reports are supported by independent genetic linkage and association data from multiple populations (Chubb et al., 2008; Bradshaw et al., 2012).

It is becoming increasingly apparent that major psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder have at least some genetic risk factors in common (Thomson, Duff et al., 2016).

As no single gene is known to be directly causative in the aetiology of major mental illness, linkage and association studies have been helpful by way of widening the search.

Large collaborative genome-wide association studies (GWAS) have shown a polygenic component to the risk of schizophrenia (McIntosh et al., 2013) and have begun to reveal the complex genetic architecture involved in psychiatric disorders. New findings from these studies have also identified an element of genetic overlap between schizophrenia, bipolar disorder and major depressive disorder (Thomson et al, 2014).

Polygenic theory (numerous genes of small effect) however, is not new. In 1967 Gottesman and Shields stated that polygenic theory had not been given enough attention, and they hypothesised that a number of genes of small effect interacting with each other, together with environmental 'milieu' pre-disposed people to the risk of developing major mental illness. Their work proposed a 'liability to schizophrenia threshold' that once reached, would most likely lead to illness.

Taking polygenic theory forward, polygenic risk scores can be calculated and therefore compared to determine whether the polygene approach could be used as a valid predictor for the later development of major mental illness (Purcell et al., 2009).

Polygenic risk for schizophrenia was investigated with a specific focus on general intelligence in a large cohort of older non-psychiatric participants by McIntosh et al., (2013) who reported an association between an increased polygenic risk for schizophrenia with lower cognitive ability at age 70. McIntosh et al., also reported that between the ages of 11 and 70 there was a greater relative decline in general cognitive ability. They concluded that common genetic variants could underlie the risk of schizophrenia as well as cognitive ageing.

Whalley et al., (2016) investigated polygenic risk for schizophrenia in depression and reported a significant relationship between neuroticism in unaffected control participants and polygenic risk for schizophrenia.

Their study did not find the same relationship in those with major depressive disorder and suggested this could be due to heterogeneity, however their findings are in line with a model in which traits for depression in the general population are predicted by genetic risk for schizophrenia. Previous studies have also reported a negative relationship between polygenic risk for schizophrenia and cognitive function, pointing to a shared genetic risk between impaired cognition and schizophrenia (Lencz et al., 2014, Liebers et al., 2016).

Polygenic risk for schizophrenia is a risk factor for schizophrenia, bipolar disorder and depression. As the *DISC1 t*(1;11) balanced translocation is not always associated with illness, let alone schizophrenia, it may be the case that polygenic risk interacts with translocation status to influence diagnosis.

1.6.2 Why is the *DISC1 t(*1;11) balanced translocation of interest and what do we know so far?

The balanced translocation itself - which identified *DISC1* – remains very much unstudied as this particular translocation has only been found in one large Scottish kindred. Single family studies are important for identification of the group of psychoses in which single-gene loci may have a major effect on illness risk (Blackwood et al., 2001). From the early work by Jacobs et al., (1970) and St. Clair et al., (1990) there is evidence that the translocation is highly heritable, at the time being found in four generations of the family.

From a study by Blackwood et al., (2001) pre-morbid I.Q. was found to be within normal ranges in both translocation carriers and non-carriers. P300 amplitude and latency, however, were found to be abnormal in family members with psychoses and their asymptomatic relatives, compared to patients with schizophrenia and healthy controls.

These findings indicate the possibility that the translocation may play a role in the development of grey matter volume in the left posterior superior temporal gyrus (STG) which has previously been found to be reduced in schizophrenic patients with auditory P300 abnormalities (McCarley et al., 1993).

Abnormal P300 amplitude and latency is also believed to indicate impairment in the speed and processing of stimuli which has been clearly demonstrated in significantly reduced information processing speed tasks in patients with schizophrenia (Braff, 1993). The *t*(1;11) translocation may also be a significant contributor here.

1.6.3 *DISC1 t*(1;11) Translocation – What is not there?

Measures of attention and pre-morbid I.Q. were obtained circa 1990 (see Chapter 2 for a full review), however a full battery of neuropsychological measures has not as yet been undertaken. Similarly, there is potential to learn more about the translocation from the wide range of imaging modalities now available (see Thomson, Duff et al., 2016).

Investigating the polygenic risk profiles of *t*(1;11) family members by directly comparing those with and without the translocation is also a promising area for future research as is the longitudinal comparison of cognitive ability, especially with regard to cognition across the lifespan, which could offer new insights.

Specific comparisons of the cognitive profiles, clinical symptoms, polygenic risk profile scores and self-reported personality/mood data between those with schizophrenia with/without the translocation; those with bipolar disorder with/without the translocation and those with major depressive disorder with/without the translocation could all be very informative.

Finally, it would also be interesting to investigate whether any cognitive domains, clinical symptoms, polygenic risk profiles and/or any self-reported questionnaire data correlate with *t*(1;11) carrier status and/or diagnosis within these family members.

1.7 Overall Aims and Hypotheses

1.7.1 *DISC1 t*(1;11) Translocation Carriers and Non-Carriers

The aim of this study - as part of a larger study undertaken to conduct complementary investigations in individuals from the *t*(1;11) family (Thomson, Duff et al., 2016), is to compare the cognitive profiles (including clinical ratings, polygenic risk profile scores and self-reported personality/mood data) of those with the genetic risk factor - *DISC1* translocation - with and without psychiatric illness and assess the effects of possible confounding factors including, in particular, illness and medication, to establish how the cognitive profiles differ and the impact, if any, of the unique balanced translocation. Group comparisons will therefore be conducted between those with and without the known genetic risk factor. Translocation carriers will then be examined by sub-group (grouped by diagnosis - with and without psychotic/affective/any psychiatric illness) with a view to determining whether any differences within this kindred could be postulated as being a translocation effect or an effect of illness.

As a result of previous findings (Blackwood et al., 2001), we hypothesise a reduction in current IQ and information processing speed in those carrying the *DISC1 t*(1;11) translocation and particularly in those with psychosis.

As positive symptom severity was found to correlate with reduced cortical thickness (Thomson, Duff et al., 2016), symptom severity, in particular positive symptoms, were also hypothesised to be associated with a reduction in IQ and measures of processing speed, again particularly in translocation carriers – especially those with psychosis.

The *t*(1;11) translocation is not always associated with illness, let alone schizophrenia, and polygenic risk for schizophrenia is a risk factor for schizophrenia, bipolar disorder and depression, it may, therefore, interact with translocation status to influence diagnosis.

As a result of this and the previous findings by McIntosh et al., (2013) and Whalley et al., (2016) it was further hypothesised that associations would be found between polygenic risk for schizophrenia in *t*(1;11) family members - especially in translocation carriers with psychosis - and measures of general intelligence (I.Q). It was also hypothesised that associations would be found between polygenic risk for schizophrenia, especially in translocation carriers with psychosis, and symptom severity - in particular positive symptomology.

The analysis plan includes examining the effects of the translocation in *t*(1;11) carriers and non-carriers and relating any findings to unaffected controls versus participants with schizophrenia and bipolar disorder. A direct comparison between translocation carriers and unrelated individuals with schizophrenia, bipolar disorder or unaffected control participants was not warranted given differences in degrees of relatedness and shared environmental effects between these groups.

Research into how similar family members' brains are has suggested that certain areas are highly heritable (Glahn et al., 2007b). This means that direct comparisons between members of one family with a group of unrelated individuals would be significantly confounded by the shared heredity within the family, therefore, direct comparisons between the *t*(1:11) kindred and those with schizophrenia, bipolar disorder or unaffected control participants were not performed.

The recruitment of schizophrenia, bipolar disorder and unaffected control participant groups allows for the comparison of the effects of having a psychiatric disorder in general, to the effects of the *t*(1;11) translocation within the family, while minimising key confounds and without the need for direct comparisons between family members and patients.

1.7.2 Aims and Hypotheses – Patients and Control Participants

In line with the investigations between *DISC1 t*(1;11) family members, the clinical, cognitive, polygenic risk profiles and self-reported personality/mood data of participants with schizophrenia, participants with bipolar disorder and unaffected control participants, will also be compared. These samples were recruited with a view to identifying any potential patterns in the results from the *t*(1;11) kindred that are absent in the patient/control groups which may be explained as being unique and potentially directly attributable to the translocation.

It was hypothesised that there would be a significant reduction in IQ and measures of processing speed between participants with schizophrenia and bipolar disorder compared to unaffected control participants and that there would be reductions in IQ and measures of processing speed between the schizophrenia/bipolar disorder participant groups with the greatest impairment in individuals with schizophrenia compared to individuals with bipolar disorder. It was similarly hypothesised that IQ in participants with bipolar disorder would be more impaired than that evidenced in unaffected control participants.

In line with the *t*(1;11) family, it was further hypothesised that associations would be found between polygenic risk for schizophrenia and general intelligence (IQ) and/or symptom severity - particularly positive symptomology - in participants with schizophrenia.

Chapter 2: The Neuropsychology of *DISC1* in Humans: A Narrative Summary

2.1 Introduction

Schizophrenia is a complex mental illness first conceptualised over 100 years ago, the cause(s) of which remains unknown. There is still no direct diagnostic test for the illness and importantly there is still no overall cure. There is, however, convincing evidence that schizophrenia is a genetic and neurodevelopmental disorder (Sawa and Snyder, 2002; Stahl, 2007).

Schizophrenia is defined by its' 'positive' symptoms (e.g. hallucinations, delusions, disordered speech and thoughts, etc.) and 'negative' symptoms (e.g. poverty of speech, inability to experience pleasure, lack of motivation, etc.) (Sawa and Snyder, 2002; Camargo et al., 2007) - positive symptoms being abnormal by their presence and negative symptoms notable by their absence. Impaired cognition is also a core symptom of schizophrenia, especially general intelligence, memory and executive functions (Johnstone et al., 2010). Research to identify new therapeutic targets for treatment, as well as to pinpoint specific indicators allowing early intervention would be beneficial in improving outcomes and helping to shield people from having to experience psychosis.

2.1.1 Schizophrenia – highly heritable and cognitive

Specific genetic markers have been identified in patients with schizophrenia and bipolar disorder. Importantly, these markers have also been identified in the non-affected relatives of patients, providing strong evidence that these illnesses are both heritable conditions (Sullivan et al., 2003; Kieseppa et al., 2004; Harrison & Weinberger, 2005, Stefansson et al., 2009).

Compelling evidence from a number of family; twin and adoption studies also report that genetic factors are important in how schizophrenia is transmitted (Johnstone et al., 1999; Harrison & Weinberger, 2005), however, this does not explain all of the variance in liability to the illness; therefore environmental factors must also be considered (Gottesman, 1991).

Cognitive bio-markers of risk have also been reported in people with schizophrenia and bipolar disorder (Keri et al., 2001; McIntosh et al., 2005; Arts et al., 2008, Drysdale et al., 2013). General intelligence (I.Q.) and working memory were found to have the highest heritability in a twin study which used genetic model fitting (Toulopoulou et al., 2007). The study also reported that genetic influences substantially contributed to all cognitive domains tested. Much work remains to be done in this area which is very promising for future studies.

2.1.2 Cognition as a possible intermediate phenotype?

Cognition, or mental processing, is essential for gaining and understanding knowledge from the world around us. Executive function, learning and memory, working memory, attention and concentration, motivation, general intellectual ability and emotions are all basic cognitive functions of the brain which can be disrupted in psychiatric illness by many factors including genetic; developmental and environmental (Lönnqvist, 2010). Intact cognition affords people the opportunity to perform and enjoy their daily routines, develop employment skills, enjoy socialising with family and friends, become motivated to set and achieve goals, enjoy sports and/or other hobbies and generally become a productive member of society. Impaired cognition can drastically impact on these abilities, however in the case of schizophrenia, and to a lesser extent, bipolar disorder, activities which are taken for granted by most, can become impossible. The level of cognitive impairment in schizophrenia can be predictive of functional abilities in areas such as living status, occupational and social abilities (Barch & Keefe, 2010; Lönnqvist, 2010).

Improving cognitive function would potentially improve the functional outcomes and quality of life for sufferers of this very debilitating illness, and go some way to addressing important humanitarian and public health concerns (Barch & Keefe, 2010).

Studies investigating cognition are gradually teasing out links between brain and behaviour with a particular focus on how to measure cognitive function in schizophrenia (Nielsen et al., 2011).

Although cognitive functions have been measured as part of many earlier studies, no standard battery of neuropsychological tests existed, meaning a wide variety of tests were used and results were therefore difficult to compare (Nielsen et al., 2011). Overall, test scores of patients with schizophrenia are likely to be one to two standard deviations below those of control subjects and those with schizophrenia have also been found to be more severely impaired than those with bipolar disorder or recurrent major depression across a wider range of cognitive domains (Nielsen et al., 2011). Imaging techniques have added valuable knowledge to the evidence base and functional imaging has consistently revealed a reduction in prefrontal cortex activity in schizophrenia - consistent with cerebral circuitry being impaired - disrupting normal cognitive functioning (Nielsen et al., 2011).

Impaired cognitive performance is recognised as a core feature of schizophrenia, so much so that there has recently been a call for schizophrenia to be reclassified as a cognitive illness (Khan & Keefe, 2013). Patients with schizophrenia demonstrate global intellectual impairments which pre-date psychosis onset, and impairment is also found in other areas of cognition, especially attention and processing speed, executive function and memory (Johnstone et al., 1999).

Information processing speed is of particular importance as it is known to account for 25% of the variance in the general ability of healthy populations (Joyce, 2013). It is evident from replicated studies that prior to the onset of psychosis, individuals who developed schizophrenia performed worse in school tests and/or IQ tests than their healthy peers, and their underperformance was evident as far back as childhood (Joyce, 2013).

As cognitive underperformance has been evidenced in schizophrenic patients as far back as childhood it is possible that this impairment is present at birth (Khan & Keefe, 2013). It is equally possible, however, that impairment occurs at some point during development, but prior to the onset of psychosis, and this lag in brain development may be a crucial early manifestation of the illness (Khan & Keefe, 2013).

Cognitive ability has been reported as being a true endophenotype for susceptibility to schizophrenia (Lencz et al., 2014), however to date, there is no defining 'cognitive signature' of schizophrenia and future research to further characterise this is promising for future work (Joyce, 2013).

2.1.3 Why might *DISC1* impact on neuropsychological function?

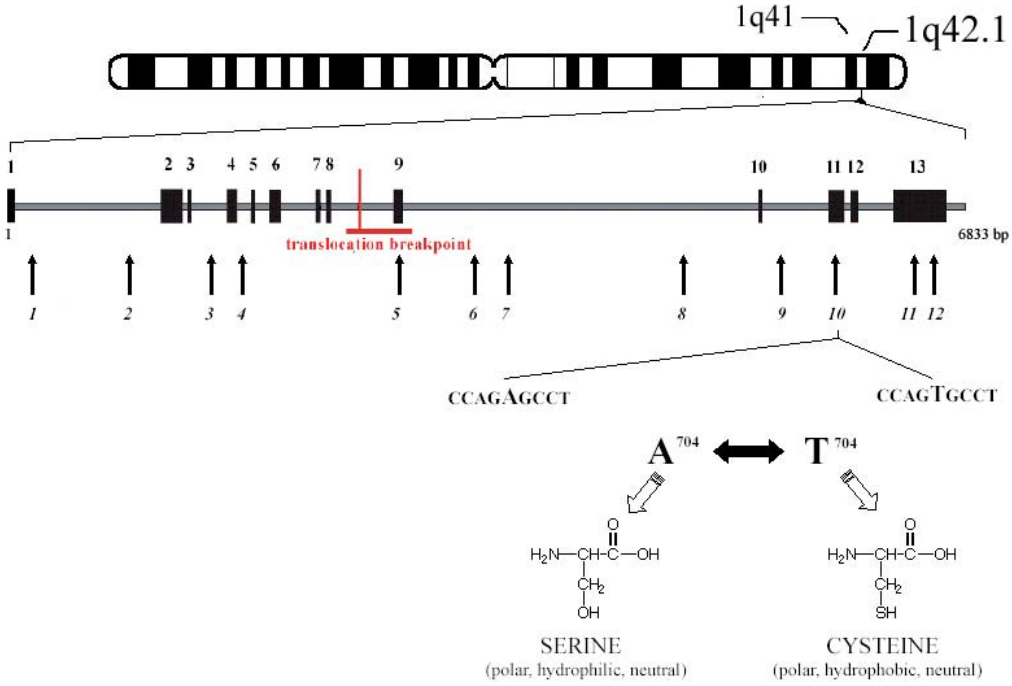
To date, it has been established that the *DISC1* gene is expressed in glia and neurons and is translated to a protein that has an impact on neurochemical and neurodevelopmental processes including neuronal migration, glutamatergic transmission, neuritic outgrowth and synaptogenesis, which are believed to be involved in the pathophysiology of schizophrenia (Cannon et al., 2005). *DISC1* is also an intracellular scaffold protein with many protein interactors (Sawa & Snyder, 2005, Ishizuka et al., 2006, Porteous & Thomson, 2006) heavily involved in critical neurodevelopmental roles.

Two of its' major roles are thought to include the regulation of key processes in early brain development and synapse formation and maintenance (Brandon & Sawa, 2011). *DISC1* has also been found to be expressed in several brain regions including the hippocampus, hypothalamus, olfactory bulb, cerebellum, cortex and in the brainstem after birth. Importantly, *DISC1* has been found to be highly expressed in the developing brain (Schurov et al., 2004). Although this gene appears to play a critical role in early development and adolescence, it is also highly expressed in the adult brain, in particular in the dentate gyrus of the hippocampus (Austin et al., 2004).

Genomic imaging studies examining the effects of *DISC1* variants on brain structure and neurocognitive function (see Duff et al., 2013 for a comprehensive review) have also provided some evidence that intact cognition is dependent on normal undisrupted development. Research over the past decade has established many critical brain mechanisms involving *DISC1* that could potentially result in abnormalities of the neurodevelopmental process, which in turn could lead to altered brain structures and/or impairment in brain function (Rampino et al., 2014).

Genetic research of *DISC1* has moved to finer mapping techniques in the search for likely single nucleotide polymorphisms (SNPs) which are responsible for transmitting the correct coding instructions in development. Two common SNPs have been studied extensively with regard to the *DISC1* gene and major psychiatric disorders, namely Ser704Cys (rs821616) and Leu607Phe (rs6675281) (Figure 2.1), see Johnstone et al., 2011 for a comprehensive review.

Figure 2.1



Copy number variants (CNVs) and rare variants are also of interest, as they are believed to play a crucial role in neurodevelopment, while collaborative genome-wide association studies (GWAS) and linkage studies have identified rare mutations and deletions in individuals, as well as duplications of genetic structures and translocations, all of which play a critical role in development, which may shed more light on the complex systems involved in normal human development free from psychiatric disorder (Bradshaw & Porteous, 2012).

Interest in the neuropsychological study of major mental illness as the link between brain and behaviour is increasing. This chapter will review the literature on the neuropsychology of *DISC1* in humans, and summarise studies that investigate cognitive function and variants of the *DISC1* gene to identify associations between *DISC1* and any specific cognitive domains that may be differentially impaired or unimpaired to help guide future research.

2.2 Methods

Studies were sought on healthy participants and/or those with psychiatric illness presenting original data on the effects of any *DISC1* gene variant and cognition. A systematic search was conducted for papers published until the end of December 2014 using Embase, PsychINFO, OVID and Pubmed. Key-words used were: Disrupted-in-Schizophrenia 1, *DISC1,* Neuropsychology, Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Cognition and Human. A manual search of the reference lists of identified review articles and bibliographic cross-referencing was also performed, together with a search of relevant conference abstracts for the period January 2010 – December 2014. From included studies, data was extracted on subject demographics, diagnosis, illness variables and neuropsychological assessments – details are provided in Tables 2.1 and 2.2.

2.2.1 Description of studies

Twenty-six human neuropsychological studies of *DISC1* or the *DISC1* location were found: (Blackwood et al., 2001 ; Gasperoni et al., 2003 ; Paunio et al., 2004 ; Hennah et al., 2005 ; Cannon et al., 2005 ; Callicott et al., 2005 ; Burdick et al., 2005 ; Thomson et al., 2005 ; Liu et al., 2006 ; Hashimoto et al., 2006 ; Palo et al., 2007 ; Di Giorgio et al., 2008 ; Raznahan et al., 2010 ; Prata et al., 2010 ; Nicodemus et al., 2010 ; Brauns et al., 2011 ; Sprooten et al., 2011 ; Chakirova et al., 2011 ; Carless et al., 2011 ; Chakravarty et al., 2012 ; Li et al., 2012 ; Kahler et al., 2012 ; Whalley et al., 2012 ; Thomson et al., 2013 ; Thomson et al., 2014 ; Nicodemus et al., 2014).

Fourteen studies specifically investigated *DISC1* variants with neuropsychological function at an observable behavioural level: (Blackwood et al., 2001; Gasperoni et al., 2003; Paunio et al., 2004; Hennah et al., 2005; Cannon et al., 2005; Callicott et al., 2005; Burdick et al., 2005; Thomson et al., 2005; Liu et al., 2006; Palo et al., 2007; Carless et al., 2011; Thomson et al., 2013; Thomson et al., 2014; Nicodemus et al., 2014).

These studies examined the effects of either the 1q42 region, the common *DISC1* SNP Ser704Cys (rs821616), other common or rare variants and gene-gene interactions with a variety of cognitive functions and are included for review (Table 2.1). Twelve studies were conducted using functional magnetic resonance imaging and were not included for review. Studies that included a measure of either current IQ, premorbid IQ and/or reading comprehension are summarised in Table 2.2.

2.2.2 Subject characteristics

From included studies, three examined healthy/non-psychiatric participants (Thomson et al., 2005; Carless et al., 2011; Thomson et al., 2013) while the majority of studies examined patients with schizophrenia and/or affective disorders (n=10). Group sizes for studies specifically examining cognition at an observable behavioural level varied from 12 to over 700 participants. Two studies specifically examined patients with schizophrenia and/or affective disorders; (Burdick et al., 2005; Liu et al., 2006) and nine studies included a comparison group of healthy control subjects (Blackwood et al., 2001; Gasperoni et al., 2003; Paunio et al., 2004; Hennah et al., 2005; Cannon et al., 2005; Callicott et al., 2005; Palo et al., 2007; Thomson et al., 2014; Nicodemus et al., 2014).

Twelve studies did not specifically examine cognition at an observable behavioural level but gathered a measure of general intelligence.

Group sizes varied from 53 to over 1000 participants (Hashimoto et al., 2006; Di Giorgio et al., 2008; Raznahan et al., 2010; Nicodemus et al., 2010; Prata et al., 2010; Sprooten et al., 2011; Brauns et al., 2011; Chakirova et al., 2011; Chakravarty et al., 2012; Li et al., 2012; Whalley et al., 2012; Kahler et al., 2012).

In general, diagnosis was confirmed by structured clinical interview for DMS-III-R and/or DSM-IV. In most cases, assessments of contemporaneous mental state were presented using observer rating scales for positive and negative symptoms of schizophrenia and some also included observer mood rating scales. Although details of antipsychotic medications were not provided, one study explicitly excluded subjects with substance misuse (Nicodemus et al., 2014), and one study included illicit substance using participants (Cannon et al., 2005).

2.3 Results

2.3.1 *DISC1* and Neuropsychological Function

To date, fourteen human neuropsychological studies of *DISC1*- using a range of assessments - include a specific measure of cognitive assessment (see Table 2.1). Twelve studies did not specifically investigate cognitive function at an observable behavioural level but did obtain a measure of either current/pre-morbid I.Q. or reading comprehension from their study samples (see Table 2.2 which includes 3 studies from Table 2.1 who also reported a measure of either current or premorbid I.Q. and/or reading comprehension). I.Q. data were not comparable due to the variability of the measures used and the methods of acquiring and reporting results.

Results have been ordered by cognitive domain as agreed by the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) (Nuechterlein et al., 2008).

Table 2.1

Studies investigating associations between DISC1 variants and specific measures of cognitive function/studies that include a specific measure of cognitive assessment.

Study	Cognitive Findings	Population	Diagnosis	*DISC1* Region / Variant	Test(s) Used*
Blackwood et al., 2001	Information Processing Speed	Scottish	1.Schizophrenia 2.Bipolar Disorder 3.MDD	*t*(1;11)	P300 Event Related Potential (ERP)
Gasperoni et al., 2003	Spatial working memory	Finnish	1.Schizophrenia	Chromosome 1q	WMS Visual Span subtest
Paunio et al., 2004	Semantic clustering and verbal learning Intrusive recall errors	Finnish: Internal Isolate (IS) Elsewhere in Finland (AF)	1.Schizophrenia families	1q32 – 1q42	CVLT
Callicott et al., 2005	Reduced performance: Logical memory Lower scores: Working memory	North American	1.Schizophrenia 2.Unaffected sibs 3.Healthy Controls	Ser704 (rs821616)	Logical Memory II (WAIS) WCST
Burdick et al., 2005	Rapid visual search Verbal working memory	African American	Schizophrenia	HCV12001930 (rs2255340) and hCV1650649	TMT-A CVLT
Cannon et al., 2005	Impaired long-term memory Impaired spatial working memory	Finnish	1. Twin pairs concordant for Schizophrenia.	HEP1 HEP2/3	CVLT WAIS-R Spatial Span CPT

	Visual Reaction Time		2. Discordant for Schizophrenia. 3. Control Pairs.	*DISC1/TRAX* Haplotype 'AATG'	
Hennah et al., 2005	Visual working memory Visual Attention	Finnish	1. Parents. 2. Affected Offspring. 3. Unaffected Offspring.	HEP3 HEP3	WMS-R Visual Span Backward Subtest WMS-R Visual Span Forward Subtest
Thomson et al., 2005	Abnormal cognitive ageing	Scottish	1.Healthy Older Adults	Cys704 (rs821616)	MHT
Liu et al., 2006	Sustained attention deficits	Taiwanese	1. Schizophrenia 2. Schizoaffective 3. Non-affective Psychoses	rs2793092-rs2793091	CPT
Palo et al., 2007	Verbal Fluency. Visuospatial ability. Psychomotor Processing Speed, Verbal ability, Visuospatial ability, visual attention, visual & verbal working memory. Perseverative Recall Errors and Long Delay Recall. Auditory attention.	Finnish	1.Bipolar Spectrum Disorders and Psychotic Disorders	rs821616 rs980989 rs751229 Protective haplotype G-T-G of rs1655285, rs751229, rs3738401	Category fluency (animal naming) WAIS-R Block Design. WAIS-R Digit Symbol, WAIS-R Vocabulary, WAIS-R Block Design, WMS-R Visual Span forward, WMS-R Visual Span backwards and Digit Span backwards. CVLT WMS-R Digit Span
Carless et al., 2011	Spatial Working Memory	Mexican-American	Non-Psychiatric	rs2793094	STAN
Thomson et al., 2013	Age of Onset	Scottish	Non-Psychiatric	TG Haplotype	Various measures as used in the Lothian Birth Cohort
Thomson et al., 2014	General Cognitive Ability	Scottish	1. Schizophrenia 2. Bipolar Disorder 3. rMDD 4. Healthy Controls	DISC1 locus	MHT
Nicodemus et al., 2014	Verbal Fluency	American	Schizophrenia Unaffected Siblings Healthy Controls	rs12133766	CVLT

** WAIS-R (Wechsler Adult Intelligence Scale Revised), WMS (Wechsler Memory Scale), WMS-R (Wechsler Memory Scale Revised), CPT (Continuous Performance Test), CVLT (California Verbal Learning Task), WCST (Wisconsin Card Sorting Task), TMT-A (Trail Making Task A), STAN (The South Texas Assessment of Neurocognition), MHT (Moray House Test No.12).*

Table 2.2

Studies that obtained a measure of current/premorbid intelligence (I.Q.) or reading comprehension.

Study	*DISC1* Region / Variant	Number (Gender)	Diagnosis / Status	Current I.Q. M (SD)	Pre-morbid I.Q. M (SD)	Reading Comp.
Blackwood et al., 2001*	***t*(1;11)**	12 10	T/L Carriers Non-carriers		100.30 100.50	
Thomson et al., 2005*	**Ser704Cys:** Cys allele Cys allele	 17(F) 13(M)	 Healthy (aged) Healthy (aged)	 93.6 106.3		
Callicott et al., 2005*	**Ser704Cys:** Ser/Ser Ser/Cys Cys/Cys	Total: 37(M)/49(F) 34(M)/27(F) 7(M)/3(F)	 Healthy Healthy Healthy	 107.7 (8.0) 109.1 (9.3) 107.8 (8.5)		107.8 (10.1) 107.2 (9.5) 112 (7.1)
Hashimoto et al., 2006	**Ser704Cys:** Ser/Ser Cys	Total: 108 86 22	 Healthy Healthy	 111.8 (11.5) 109.2 (13.7)		
Di Giorgio et al., 2008	**Ser704Cys:** Ser/Ser Cys carriers	Total: 80 13(M)/26(F) 13(M)/28(F)	 Healthy Healthy	 113.5 112.2		
Prata et al., 2010	**Ser704Cys:** Ser/Ser Cys Ser/Ser Cys Ser/Ser Cys	Total: 16(M)/5(F) 20(M)/3(F) 6(M)/11(F) 8(M)/10(F) 14(M)/12(F) 12(M)/15(F)	 Schizophrenia Bipolar Disorder Healthy Controls 	 101.44 (16.23) 94.00 (15.57) 109.87 (13.16) 103.35 (17.44) 118.63 (8.19) 115.05 (15.89)		
Nicodemus et al., 2010	***DISC1 x CIT*** rs1411771 x rs10744743	 Total: 217 100(M)/117(F)	 Healthy	 109.0		
Raznahan et al., 2010	**Ser704Cys** Ser/Ser Cys **Leu607Phe** Leu/Leu Phe	 67(M)/57(F) 80(M)/51(F) 107(M)/86(F) 40(M)/22(F)	 Healthy Healthy Healthy Healthy	 113 (12.2) 114 (12.2) 113 (12.3) 114 (11.7)		
Chakirova et al., 2011	**Ser704Cys**	Total: 89 13(M)/7(F) 20(M)/16(F) 18(M)/15(F)	 Schizophrenia Bipolar Disorder Healthy Controls		 107.8 111.3 113.3	
Brauns et al., 2011	**Ser704Cys:** Ser/Ser Cys **Leu607Phe:** Leu/Leu Phe **rs1322784:** T/T C **rs11122459:** G/G A **Arg264Gln:** Arg/Arg Gln	Total: 97 28(M)/27(F) 24(M)/14(F) 45(M)/27(F) 11(M)/13(F) 38(M)/24(F) 18(M)/17(F) 27(M)/19(F) 29(M)/22(F) 24(M)/18(F) 25(M)/22(F)	 Healthy Healthy Healthy Healthy Healthy Healthy Healthy Healthy Healthy Healthy			 51.04 50.18 50.60 50.75 50.89 50.56 51.15 50.27 49.79 51.19

Sprooten et al., 2011	**Ser704Cys** A/A A/T T/T	Total: 87 17(M)/22(F) 16(M)/22(F) 6(M)/4(F)	 Healthy Healthy Healthy	 113 (2.11) 111 (2.26) 119 (3.00)		
Whalley et al., 2012	**Leu607Phe:** Leu/Leu Phe carriers	Total: 18(M)/19(F) 25(M)/29(F) 24(M)/35(F) 2(M)/8(F) 15(M)/15(F) 11(M)/8(F)	 Scz High Risk Bipolar High Risk Healthy Controls Scz High Risk Bipolar High Risk Healthy Controls	 	 102.14(10.16) 107.74 (8.78) 111.19 (8.79) 97.80 (8.18) 112.77 (7.40) 110.10(4.75)	
Li et al., 2012	**Ser704Cys:** Ser/Ser Cys	Total: 198 94(M)/104(F) 32(M)/48(F)	 Healthy Healthy	 116.84 (9.822) 117.41 (8.138)		
Chakravarty et al., 2012	**Ser704Cys:** Ser Cys/Cys **Leu607Phe:** Phe Leu/Leu	Total: 54 12(M)/9(F) 21(M)/12(F) 6(M)/3(F) 27(M)/18(F)	 Healthy Healthy Healthy Healthy	 116.5 (9.01) 116.3 (8.9) 116.0 (12.8) 116.5 (8.0)		
Kahler et al., 2012	***DISC1* SNPs**: rs821589 rs11122319 rs1417584	Total: 355 89(M)/82(F) 100(M)/84(F)	 Healthy Controls Psychosis Patients: (schizophrenia, schizoaffective, schizophreniform bipolar 1, bipolar NOS, bipolar II, major depression with psychosis, psychosis NOS)	 115.0 (9.3) 107.5 (12.4)		

*Also included in Table 2.1

2.3.2 General intellectual ability (I.Q.)

Blackwood et al., (2001) measured general intellectual ability in all participating members of a large extended Scottish kindred, some of whom carried a unique *t*(1;11) translocation. Using the National Adult Reading Test (NART), pre-morbid intelligence scores were found to be within the normal range and no differences were found in mean pre-morbid I.Q. scores between translocation carriers (n=12, M=100.3) and non-carriers (n=8, M=100.5). A measure of current I.Q. in this study would have allowed pre-morbid I.Q. to be compared to current I.Q. which may have revealed an effect of the translocation.

As a result of its association with impaired learning and memory, variation in *DISC1* became the focus of normal cognitive aging. Thomson et al., (2005) used the same general mental ability test undertaken by participants of the Lothian Birth Cohort in 1921 at age 11 and tested them again at age 79 to examine the effect of genotype at SNP rs821616 and normal cognitive function (n=425). Although there were no significant effects of *DISC1* genotype on cognition, a significant genotype by sex interaction was revealed for females homozygous for the Cys allele. Female (n=17) cognitive ability scores were significantly lower than males (n=13); indicating the possibility that variation in *DISC1* may affect normal cognitive aging, especially in females. This was the first study to report an association between cognitive function and a *DISC1* polymorphism in a non-psychotic population. Due to the small sample sizes these findings will require to be replicated in a larger sample before being confirmed.

In a more recent study, Thomson et al., (2014) investigated 889 control participants from the Lothian Birth Cohort (LBC) (1936) with 653 patients (schizophrenia (n=240), bipolar disorder (n=221) and recurrent major depressive disorder (n=192)).

Functional and putative regulatory variants were found to be nominally associated with recurrent major depressive disorder and/or cognitive ability at the locus-wide level of significance. Burden analysis for putative functional variants observed a nominally significant increase in burden of minor alleles for coding SNPs or SNPs in CpG islands and Moray House Test score measures of cognitive ability. As the reported association between recurrent major depressive disorder in the discovery cohort and an intronic SNP (rs16856199) had a 'modestly significant *P*-value' which could be due to chance, these findings require to be replicated in independent samples.

In a separate population based study of participants with recurrent major depression (Generation Scotland) no significant results were found for any of the cognitive variables investigated, however Thomson et al., (2013) did report association of the *DISC1* SNP rs6541281 with a reduced age of onset.

2.3.3 Speed of Processing

The previously mentioned study by Blackwood et al., (2001) also investigated auditory P300 Event Related Potential (ERP) recordings in their study of a Scottish kindred known to carry a unique *DISC1 t*(1;11) translocation (n=12). Recordings were compared with a group of non-carriers from the same family (n=10); a group of unrelated patients with schizophrenia (n=20) and a group of healthy controls (n=26). The study detected abnormal P300 amplitude and latency in translocation carriers with psychoses and their asymptomatic relatives.

Auditory P300 is believed to indicate deficits in the speed and efficiency of the processing of stimuli in short-term memory and has consistently shown prolonged latency of, and reduced amplitude of P300 ERP in patients with schizophrenia as well as in their relatives.

Studying single large families with multiple affected family members is advantageous in mental health research, especially the major psychoses, however there is also a disadvantage in that the results could be unique and/or rare to that particular family and not, in fact, to the illness itself.

Burdick et al., (2005) provided preliminary evidence that the *DISC1* gene may affect information processing in patients with schizophrenia. In their study of 250 patients with schizophrenia, a significant association was found between the *DISC1* SNP *h*CV1650649 and rapid visual search using the Trail Making Test-A.

Patients carrying two copies of this risk allele were found to perform significantly worse than patients carrying only one or no copies, and these results remained significant after they limited their comparisons to patients carrying two copies of the risk allele (n=152) to patients carrying only one copy (n=87). Patients were split into two groups - African Americans and Caucasians - however after conducting analyses for these groups separately, only the results for the African American patients remained significant. It was noted that there were demographic differences between the groups, specifically in terms of illness duration and education which may have had a bearing on these results.

In a large study of Finnish families, Palo et al., (2007) collected neuropsychological data on 158 individuals with a range of diagnoses including Bipolar Disorder I, Bipolar Disorder II, Bipolar Disorder NOS, Cyclothymia, Bipolar Disorder 1 with intermittent psychotic features, psychotic depression, schizophrenia, schizoaffective disorder and psychosis NOS as well as unaffected family members. Using the Category Fluency task from the Controlled Oral Word Association Test, designed to assess verbal fluency, Palo et al., reported an association between category fluency and the *DISC1* SNP rs821616.

Their study also reported an association between the *DISC1* SNP rs980989 and psychomotor processing speed using the Digit Symbol task, again taken from the Wechsler Adult Intelligence Scale-revised. It should be noted that the significant results reported here were not corrected for multiple testing to afford a full interpretation using the non-corrected values.

In a recent study, Nicodemus et al., (2014) combined a candidate gene approach with a computational linguistic approach (latent semantic analysis (LSA)). Using a category fluency task (animals) the *DISC1* SNP rs12133766 was found to be negatively associated with average vector length in male controls – a finding which was replicated in male probands but not male siblings, likely due to the small sample. This finding indicates that males who carried a copy of the minor allele at rs12133766 used less complex terms in response to the cue 'animal' than those who did not carry a copy of the minor allele, regardless of the number of words generated.

Their study also found that this SNP was not significantly associated with traditional measures of verbal learning and recall which suggests the novel computational linguistic approach may be tapping into different components of category fluency than those measured by the more traditionally-used tasks, and may therefore be able to provide a more specific phenotype.

2.3.4 Attention and Vigilance

In their study of 215 Finnish families, of which 746 individuals completed comprehensive neuropsychological assessments, Hennah et al., (2005) reported an association between the *DISC1* haplotype HEP3 and visual attention and visual working memory.

Using the visual span forward task from the Wechsler Memory Scale-Revised, Hennah et al., noted a poorer performance in the affected offspring but not in the unaffected offspring for visual attention.

The included individuals had a range of diagnoses and were grouped according to increasingly inclusive liability classes (LC). LC1 comprised individuals with schizophrenia only; LC2 included individuals with schizophrenia and schizoaffective disorder; LC3 included individuals with schizophrenia, schizoaffective disorder and schizophrenia spectrum disorders and finally, LC4 represented the whole sample with the addition of individuals with bipolar disorder and/or major depressive disorder and 356 unaffected offspring. This finding is slightly unexpected as earlier work by Hennah et al., 2003 postulated the HEP3 haplotype as a potentially protective variant.

Cannon et al., (2005) examined gene-gene interactions involving *DISC1* variants in 7 twin pairs concordant for schizophrenia, 52 twin pairs discordant for schizophrenia and 59 healthy control twin pairs (n=236). Their work reported associations between a rare 4-SNP *DISC1/TRAX* haplotype, 'AATG' (n=17) which was significantly positively associated with visual reaction time. A primary difference was reported between the two samples in the genetic structure of the HEP2 haplotype (AC) which was found to have a lower-than-expected rate in the twin sample. This finding could indicate the variation as being due to chance, especially in view of the small sample size.

102 schizophrenic nuclear families with at least 2 affected siblings were assessed using a Continuous Performance Task (CPT) by Liu et al., (2006). 231 individuals were assessed using an un-degraded CPT task and 225 completed a degraded CPT task. Liu et al., reported an association between *DISC1* and impairment of sustained attention suggesting the *DISC1* gene may be involved in regulating the working memory aspect of sustained attention in schizophrenia.

As the significant finding was associated with the un-degraded CPT task and not the degraded task, it's possible that this task makes use of differing neuropsychological functions, i.e. the degraded task involves working memory together with a sensory-perceptual component, whereas the un-degraded task involves working memory only.

2.3.5 Working Memory

Early work by Gasperoni et al., (2003) reported an association between variation in spatial working memory in schizophrenic patients and their unaffected co-twins, with a marker on chromosome 1q. Their study sample consisted of 30 dizygotic and 20 monozygotic same-sex twin pairs discordant for schizophrenia, and 27 dizygotic and 28 monozygotic healthy control twin pairs. Generalizability of this result may be questionable due to the fact that the data relate to a genetic isolate from Finland, therefore additional research using non-Finnish populations is required to confirm this finding.

As part of their larger *DISC1* imaging study, Callicott et al., (2005) assessed working memory separately using the Wisconsin Card Sorting Task.

At an observable behavioural level they reported lower category scores for homozygous Ser allele (rs821616) participants across all diagnoses. Although this result reached significance, it did not survive multiple comparisons. It was noted in this study that *DISC1* had a larger impact on MRI findings as oppose to the observable behavioural cognitive findings and it's possible that *DISC1* variation may impact the efficiency of information processing, resulting in mild neuronal impairment rather than more pronounced cognitive deficits.

In the previously mentioned study of 250 patients with schizophrenia by Burdick et al., (2005) verbal working memory was found to be significantly associated with the *DISC1* SNP *h*CV1650649 using the Digits Backward task.

Again, patients carrying two copies of this risk allele were found to perform significantly worse than patients carrying one or no copies of the allele and again, these results remained significant after limiting their comparisons to patients carrying two copies of the risk allele (n=152) to patients carrying only one copy (n=87). Patients were split into two groups - African Americans and Caucasians - however after conducting analyses for these groups separately, only the results for the African American patients remained significant. Previous studies with positive findings were restricted to Caucasian subjects, therefore having distinct ethnic groups could have resulted in environmental effects and/or the effects of other genes differentially modulating this relationship.

In their population-based cohort study of same-sex twins born in Finland, Cannon et al., (2005) tested for associations between schizophrenia and several endophenotypic traits believed to be involved in the pathogenesis of this illness. Using the Wechsler Memory Scale, a 4-SNP *DISC1/TRAX* haplotype (AATG; n=17) was found to be associated with spatial working memory. Again, it was previously noted that there was a primary difference between the two samples in the genetic structure of the HEP2 haplotype (AC) which was found to have a lower-than-expected rate in the twin sample. This finding could indicate the variation as being due to chance, especially in view of the small sample size.

Using the Wechsler Memory Scale-revised (Digit Span Forward), Palo et al., (2007) reported an association between a *DISC1* protective haplotype: G-T-G of rs1655285, rs751229 and rs3738401 and auditory attention as part of a study of 158 individuals from Finnish families with Bipolar Disorder. Participants included unaffected family members (n=51), participants with other mental disorders (n=26) and an overlapping sample of participants with bipolar disorder type 1, type II, NOS and cyclothymia.

These participants also overlapped with bipolar disorder participants with intermittent psychotic features, psychotic depression, schizophrenia, SA disorder and psychosis NOS (Palo et al., 2007). As previously noted, the significant results reported in this study were not corrected for multiple testing and the non-corrected values have been shown to allow for a full interpretation of the data.

Carless et al., 2011 conducted a large study utilising non-psychiatric participants from large extended families who were part of the San Antonio Family Heart Study and the San Antonio Diabetes/Gallbladder Study (n=1232). Using a spatial delayed response task they reported cognitive measures of working memory as being associated with the *DISC1* SNP rs2793094 and spatial working memory. Correction for multiple testing was not performed on all of the phenotypes examined in this study, therefore replication of the observed associations will be required.

2.3.6 Verbal Learning and Memory

Using the California Verbal Learning Test, chromosome region 1q42 was found to have linkage of semantic clustering and verbal learning in an internal isolate of 110 Finnish schizophrenia families living in northern Finland, and of intrusive recall errors in 58 Finnish schizophrenia families living elsewhere in Finland (Paunio et al., 2004).

As part of their larger *DISC1* imaging study, Callicott et al., (2005) assessed episodic memory separately using the Logical Memory II subsection of the Wechsler Memory Scale. At an observable behavioural level they reported that participants with schizophrenia, homozygous for the Ser allele of SNP rs821616 demonstrated reduced performance on this task. Although this result reached significance, it did not survive multiple comparisons.

Ser/Cys has not been implicated as being a causative mutation for diminished cognition and there is no direct evidence to this effect, therefore investigating different *DISC1* SNPs may yield stronger effects.

In their large twin-study (n=236) examining gene-gene interactions of *DISC1* variants, Cannon et al., (2005) reported associations between certain *DISC1/TRAX* haplotypes and short-term and long-term memory impairment. Using the California Verbal Learning Task, semantic clustering was significantly negatively associated with a 3-SNP *DISC1* Haplotype - HEP1 (n=115) and HEP1 was also associated with verbal learning and memory generally. A 4-SNP *DISC1/TRAX* Haplotype – AATG (n=17) was also significantly negatively associated with verbal learning and memory.

In their large study of Finnish families with Bipolar Disorder, Palo et al., (2007) also administered the California Verbal Learning Test to 158 participants (bipolar spectrum disorder (n=66); psychotic disorder (n=67); other mental disorders (n=26) and unaffected family members (n=51)) and reported an association to perseverative recall errors and long delay recall with the *DISC1* SNP rs751229. Long delay recall was also found to be associated with the *DISC1* SNP, rs1322784. It has already been noted that the significant results from this study are non-corrected due to the omission of multiple testing.

2.3.7 Visual Learning and Memory

In their previously mentioned study of 215 Finnish schizophrenia families, Hennah et al., (2005) used the visual span backward task from the Wechsler Memory Scale-Revised and reported evidence of poorer performance in visual working memory in a sample of 249 affected offspring and 273 unaffected offspring.

They noted an almost equal contribution from both the affected and unaffected offspring to their observed associations between short-term visual memory and the *DISC1* haplotype HEP3. As stated earlier, the HEP3 haplotype had previously been thought to represent a protective variant which is counterintuitive to these findings.

2.3.8 Reasoning and Problem Solving

The Wechsler Adult Intelligence Scale-revised (Block Design) was also administered by Palo and colleagues (2007) as part of their previously mentioned Finnish bipolar family study. Using this measure they reported an association between visuospatial ability and the *DISC1* SNP rs821616. Visuospatial ability was also found to be associated with the *DISC1* SNP rs980989. It has already been noted that the significant results reported in this study are based on non-corrected values due to the omission of multiple testing. Multiple testing was not conducted to allow a full interpretation of the data.

2.4 Discussion

Although general intelligence (I.Q.) could not be statistically compared across studies, premorbid I.Q. in the Scottish kindred was found to be within the normal range in both those carrying the rare *t*(1;11) translocation and those without. A measure of current I.Q. was not obtained for these family members, and is an area for future examination as it may reveal an impact of the translocation on general intelligence. The *DISC1* SNP rs821616 was reported to affect general cognition in older non-psychiatric females who had significantly lower scores on cognitive ability tests than their male counterparts (Thomson et al., 2005). Variation in *DISC1* may be a risk factor for impaired cognition in general, and for cognitive aging, especially in females.

From the fourteen studies that specifically examined *DISC1* and/or the *DISC1* region and cognitive function at an observable behavioural level, Blackwood et al., focussed on a rare *t*(1;11) translocation, three studies focussed on the *DISC1* chromosome region 1q (Gasperoni et al., 2003; Paunio et al., 2004; Liu et al., 2006), three studies investigated a common *DISC1* SNP, namely Ser704Cys (rs821616) (Callicott et al., 2005; Thomson et al., 2005; Palo et al., 2007), two studies examined *DISC1/TRAX* haplotypes (Hennah et al, 2005; Cannon et al., 2005) and five studies found associations between cognitive function and a number of other *DISC1* SNPS (Burdick et al., 2005; Palo et al., 2007; Carless et al., 2011; Thomson et al., 2014; Nicodemus et al., 2014).

Spatial working memory, verbal learning and memory and visual attention have all been associated with variation at the breakpoint region, 1q42 (Gasperoni et al., 2003; Paunio et al., 2004; Liu et al., 2006). Verbal fluency, visual memory, working memory, visuospatial ability and the Moray House Test of general cognition have been associated with the common *DISC1* SNP, Ser704Cys (rs821616) (Callicott et al., 2005; Thomson et al., 2005; Palo et al., 2007).

Verbal learning and memory, visual memory, spatial working memory, reaction time and attention have all been associated with the *DISC1* haplotypes, HEP1, HEP3, a rare *DISC1/TRAX* haplotype, 'AATG' and/or a protective haplotype G-T-G of rs1655285, rs751229 and rs3738401, (Cannon et al., 2005; Hennah et al., 2005; Palo et al., 2007). Spatial working memory was also associated with *DISC1* SNP rs2793094 (Carless et al., 200), while verbal working memory associated with *DISC1* SNPs *h*CV1650649 and *h*CV12001930 (Burdick et al., 2005). In this study, Burdick and colleagues also reported an association between processing speed and both of these *DISC1* SNPs.

Verbal fluency associated with the *DISC1* SNP rs12133766 (Nicodemus et al., 2014) and psychomotor processing speed was associated with the *DISC1* SNP rs980989 (which was also significantly associated with visuospatial ability and verbal learning) (Palo et al., 200). The rare *t*(1;11) translocation was associated with abnormal P300 results in family members which is believed to be an indication of impaired processing speed.

2.4.1 Why is the *DISC1 t*(1;11) Translocation of interest and what do we know so far?

The balanced translocation itself - which identified *DISC1* – remains very much unstudied as this particular translocation has only been found in one large Scottish kindred. Single family studies are important for identification of the group of psychoses in which single-gene loci may have a major effect on illness risk (Blackwood et al., 2001). From the early work by Jacobs et al., (1970) and St. Clair et al., (1990) there is evidence that the translocation is highly heritable, being found in four generations of the family. From the study by Blackwood et al., (2001) pre-morbid I.Q. was found to be within normal ranges in both translocation carriers and non-carriers, however, P300 amplitude and latency were found to be abnormal in family members with psychoses and their asymptomatic relatives compared to patients with schizophrenia and healthy controls.

These findings indicate the possibility that the translocation may play a role in the development of grey matter volume in the left posterior superior temporal gyrus (STG) which has previously been found to be reduced in schizophrenic patients with auditory P300 abnormalities (McCarley et al., 1993). As stated earlier, abnormal P300 amplitude and latency is also believed to indicate impairment in the speed and processing of stimuli which has been clearly demonstrated in significantly reduced information processing speed tasks in patients with schizophrenia (Braff, 1993). The *t*(1;11) translocation may also be a significant contributor here.

2.4.2 *DISC1 t*(1;11) Translocation – What is not there?

Although measures of attention and pre-morbid I.Q. were obtained circa 1990, a full battery of neuropsychological tests has not as yet been undertaken. Similarly, there is potential to learn more about the translocation from the variety of imaging modalities now available.

Direct comparisons between those with and without the translocation are promising areas for future research. Longitudinal comparisons of cognitive ability, especially with regard to cognition across the lifespan, could also offer new insights. Specific comparisons between those with schizophrenia with/without the translocation; those with bipolar disorder with/without the translocation and comparisons of those with major depressive disorder with/without the translocation could be very informative. Considering the previous work conducted by Thomson et al., (2005) which found a significant effect of genotype by gender on cognitive ability in older females, future work could potentially investigate the possibility of an effect of gender between *t*(1;11) carriers and non-carriers. It would also be interesting to investigate whether clinical symptoms and self-report questionnaire data correlate with *t*(1;11) carrier status and/or diagnosis within these family members.

2.4.3 Methodological Issues

The results from these studies appear inconsistent and the majority are limited by small sample sizes. No study presented power calculations and multiple comparisons were not routinely conducted. False negative results are likely when analysing small sample sizes and can reduce the probability of reliable positive findings – especially in association with multiple comparisons. A number of studies investigated similar populations and potential confounding factors were not fully accounted for.

Non-genetic confounders such as age and gender were most frequently controlled for, however antipsychotic medication, lifestyle, substance abuse, illness duration, affection status and years of education were not routinely accounted for. A measure of either pre-morbid or current I.Q. may also have been helpful in view of its known effect on cognition. To remedy the small sample sizes, a possible solution might have been to calculate a combined effect size estimate through meta-analysis, however this option was not viable due to the methodological differences which prevented valid meta-analysis of this data. Another inconsistency is the lack of an accepted standard battery of neuropsychological tests. Although a number of studies made use of the CVLT together with various measures from the WAIS (Wechsler Adult Intelligence Scale), there were a number of other tests used, making it difficult to compare the data. The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) test battery was primarily developed for use in clinical trials in schizophrenia to evaluate cognition-enhancing medications, however, universal use of this battery or the Brief Assessment of Cognition in Schizophrenia (Keefe, Harvey et al., 2004) would facilitate the comparison of neurocognitive data across studies (Nuechterlein et al., 2008).

2.4.4 Conclusion

DISC1 remains one of the most important and most studied genes in psychiatric research – its importance confirmed in a recent study by Ayalew et al., (2012) who identified it as one of the leading risk genes for the development of schizophrenia, based on the totality of biological evidence. Moreover, Thomson et al., (2014) made clear that many *DISC1* variants remain undiscovered. The majority of measures in the studies reviewed here included a component of working memory which is known to be impaired in schizophrenia as well as affective disorders.

Working memory and working memory subsystems (posited by Baddeley, 1986; 1992) i.e. verbal memory (*phonological loop*), visual memory (*visuospatial sketchpad*) and possibly a subsystem for numerically processed information (Leather & Henry, 1994) are reported to be mediated by prefrontal areas of the brain and invoke the dorsolateral prefrontal cortex (Callicott et al., 2000; Horn et al., 2003). It has also been reported that in schizophrenia, *DISC1* expression is altered in the orbitofrontal cortex (Sawamura et al., 2005) which is linked to the dorsolateral prefrontal cortex and working memory, prompting Burdick et al., (2005) to suggest that the orbitofrontal cortex may mediate *DISC1* effects on neurocognition. This may especially relate to the memory system, as working memory underlies a number of verbal and visual cognitive abilities (Silver et al., 2003).

Silver et al., reported that verbal working memory was significantly correlated with visual orientation, visual retention, executive function, visuomotor coordination and simple motor function. Their study also reported that spatial working memory was significantly correlated with visual orientation, visual retention, simple motor function, memory for faces and memory for objects (Silver et al., 2003). In addition to verbal and visual abilities, working memory also underlies processing speed (Brebion et al., 1998) and sustained attention (Coull et al., 1996; Liu et al., 2006) all of which have been found to associate with either *DISC1* or the *DISC1* region.

From the studies reviewed here, *DISC1*/*DISC1* SNPs and/or *DISC1* (*DISC1/TRAX*) haplotypes have shown association with a number of cognitive domains, the majority of which utilise a working memory component, supporting the current dominant neurodevelopmental hypothesis (Owen et al., 2011).

Impaired working memory is likely to have a knock-on effect on other cognitive processes such as information processing speed, verbal and visual memory functions, verbal fluency and sustained attention, all of which will, in turn, have a negative impact on measures of general intelligence (I.Q.). Future work examining the *DISC1* gene and cognition, specifically in relation to the memory system and general intelligence, are promising areas in the search for genetic variants which may underlie cognitive impairment in schizophrenia and affective disorders.

Of particular interest is the *t*(1;11) balanced translocation which may play a role in both working memory and therefore general intelligence as a result of the abnormal P300 recordings identified in this family (Horn et al., 2003). Taken together, these findings strengthen the evidence base and support the importance of the *DISC1* gene in neurodevelopment.

Chapter 3: Methodology

3. Methodology

3.1 Participants

3.1.1 Inclusion Criteria: *DISC1 t*(1;11) Carriers and Non-Carriers

Fifty members of this large previously reported Scottish kindred (St Clair, Blackwood et al., 1990) were approached to participate in the study (Figure 3.1). Members of the family had been in contact with researchers from the University of Edinburgh for many years and through them other members of the family were invited to participate. There were no specific inclusion criteria as the study required as many family members as possible to participate. The only exclusion criteria were the ability to provide informed consent and the MRI safety checklist.

All members of the family who were willing to participate (n=42) were recruited. Four married-in participants were excluded from the analysis, leaving a total of 38 and, after informed consent was obtained, whether an individual participant carried the *t*(1;11) balanced translocation was confirmed (n=14) with one unable to complete all tasks. Three subjects were diagnosed at structured psychiatric interview with a psychotic disorder (1 x schizophrenia, 1 x schizoaffective disorder and 1 x bipolar disorder). All were treated with valproate and two out of three were also treated with antipsychotic drugs (one with clozapine and lithium and one with risperidone and sertraline) (Table 3.1). All other subjects were un-medicated at the time of testing.

Full clinical diagnoses for all of the translocation carriers are as follows: Schizophrenia (n=1), Schizoaffective Disorder (n=1), Bipolar Disorder (n=1), Major Depressive Disorder (Recurrent) (n=3), Major Depressive Disorder (Single Episode) (n=3), Cyclothymia (n=3) Conduct Disorder (n=1), thus, all 13 received a diagnosis.

Clinical diagnoses were also established for three of the non-carriers as follows: Major Depressive Disorder (Recurrent) (n=2) and Generalised Anxiety Disorder (n=1). One non-carrier was also being treated with Amytriptyline (Table 3.1).

Medication for *t*(1;11) Carriers and Non-Carriers

***t*(1;11) Carrier Diagnosis**	**Medication**
Schizophrenia	Clozapine, Lithium, Valproate,
Schizoaffective Disorder	Risperidone, Valproate, Sertraline
Bipolar Disorder	Valproate
Major Depressive Disorder (Recurrent)	Fluoxetine
Non-Carrier Diagnosis	**Medication**
Depression (Single Episode)	Amytriptyline

Table 3.1 - Medication for t(1;11) Carriers and Non-Carriers

Figure 3.1 – *DISC1* *t*(1;11) Scottish Kindred

DISC1 family tree diagram. Individuals included in current analysis are highlighted in red/blue. Image created in Haplopainter.

Carriers included (n=13)
Non-Carriers included (n=15)

Y: *t*(1;11) carrier
IQ: Only Current IQ available

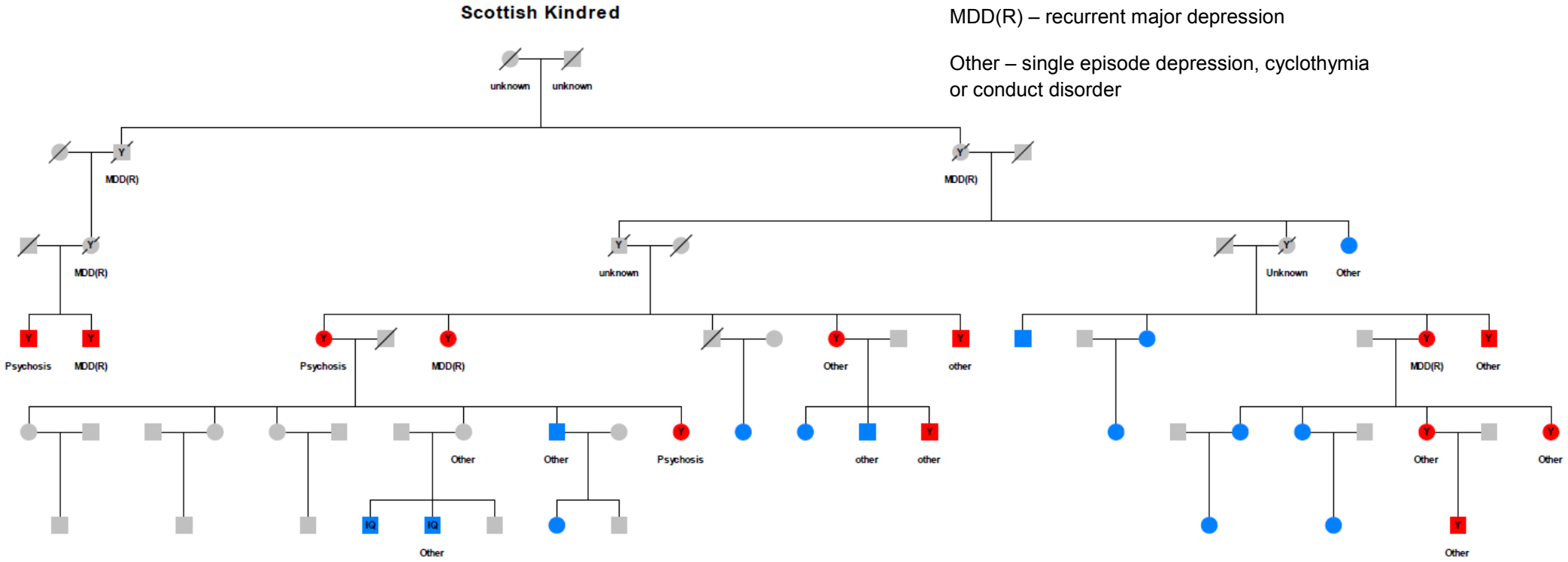
Diagnoses:

Unknown – unknown psychiatric status

Psychosis – schizophrenia, schizoaffective or psychotic bipolar disorder

MDD(R) – recurrent major depression

Other – single episode depression, cyclothymia or conduct disorder



3.1.2 Inclusion Criteria: Patients (Schizophrenia and Bipolar Disorder)

We also recruited a 'positive control' group of patients with affective and psychotic illnesses: schizophrenia (n=32) and bipolar affective disorder (n=16). The aim of recruitment of this group was to allow us to establish robust effects of the *t*(1;11) translocation within the family, and to evaluate the possibly confounding effects of having a psychotic disorder. Patients were recruited through consultant psychiatrists in Edinburgh and were then approached by the study team to give informed consent to participate in the trial. The majority of patients with schizophrenia were stable and were happy to participate in research having taken part in previous studies which may have increased the number of participants in this sample with more years of education, greater socio-economic status and higher than expected general intellectual ability. Only those who were able to provide informed consent were recruited.

3.1.3 Inclusion Criteria: Unaffected Control Participants

A group of unaffected control participants were also recruited (n=42). Where possible, control participants were recruited from the same geographical areas as the family and patient groups. Unaffected control participants were also recruited directly from the Scottish Mental Health Research Register which was set up for people who were interested in taking part in mental health research.

3.1.4 Exclusion Criteria

Exclusion criteria for all patients and unaffected controls included the following:

- Inability to give informed consent
- MRI safety exclusion criteria (metal / pacemaker)
- Dementia or other neurological disorder
- History of severe head injury (with loss of consciousness)
- Current substance dependence / a clinical diagnosis of substance-induced psychosis (although NB that current substance misuse is not an exclusion criterion)

In addition, for unaffected control participants, exclusion criteria included a family history of psychosis or other mental health disorder.

The study was approved by the Multicentre Research Ethics Committee for Scotland.

3.2 Clinical Assessments and Procedure

All participants (n = 128) were interviewed by a trained psychiatrist and diagnoses were confirmed using the SCID (First, Spitzer et al. 2002) and/or the OPCRIT symptom check-list (McGuffin, Farmer et al. 1991). All diagnoses were reviewed by a second psychiatrist who was blind to diagnosis and carrier status. Participants were further assessed using the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981), Global Assessment of Functioning (GAF) (DSM-III-R, American Psychiatric Association, 1987), Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Symptom rating took place within one week of the MRI scan.

Participants were then invited to complete a range of self-report personality and mood questionnaires which included the Beck Depression Inventory (BDI) (Beck et al., 1961), the Altman Mania Scale (AMS) (Altman et al., 1997), the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975), the TEMPS-A (Akiskal & Mallya, 1986) and the Kings Schizotypy Questionnaire (KSQ) (Williams, M. The psychometric assessment of schizotypal personality. PhD thesis. Institute of Psychiatry, University of London, 1993). Tests were administered in the same order (as above) to each participant. Full details of the clinical rating scales and self-report questionnaires used are detailed below in order of administration.

3.2.1 Clinical Measures

(a) Structured Clinical Interview for DSM-IV

The Structured Clinical Interview for DSM-IV Axis Disorders Patient Version (First, Spitzer et al., 1995) provides a semi - structured scripted approach to evaluate psychopathology and establish the current or lifetime presence of psychiatric diagnoses according to DSM - IV Criteria (American Psychiatric Association, 1994). For each specific diagnosis, e.g. depression/anxiety, mania, psychosis and/or panic, initial probe questions glean critical criteria for each disorder. Positive responses are followed up with additional questions and negative responses allow the interviewer to move forward to the next section. The SCID has good reliability, as demonstrated across many types of study (i.e., multi-site vs. single site, joint vs. test-retest, and/or with raters who have worked together, etc.). Determining validity is more difficult due to the lack of there being a 'gold standard' which could be used to establish psychiatric diagnoses (Insel, 2013) therefore the clinical standard is often the 'best estimate' diagnoses.

(b) Operational Criteria Checklist

The OPCRIT (OPerational CRITeria) is a checklist made up from the operational criteria for major psychiatric illnesses and generates diagnoses based on each DSM classification (McGuffin et al., 1991). Originally, OPCRIT was designed to be used in molecular genetic research to allow a polydiagnostic approach to be used in the diagnosis of psychotic and affective disorders (Craddock et al., 1996). The OPCRIT is made up of 90 items focussing on psychopathology together with relevant background information. The OPCRIT checklist can include information gathered from diagnostic interviews and/or case records and can be rated on an episodic or lifetime-ever basis.

The OPCRIT has good reliability and, as previously with the SCID, as there is no 'gold standard' to measure the validity of lifetime psychiatric diagnoses, the 'best-estimate' diagnosis (reached by the consensus of two or more psychiatrists (or trained clinicians) on the basis of all available information) is currently accepted as standard procedure (Leckman et al., 1982).

(c) Positive and Negative Symptoms Scale

Schizophrenia is defined by positive symptoms (hallucinations, delusions, disorganized thought) and by negative symptoms (cognitive deficits, blunted affect, impaired social functioning) (Kay et al., 1987). The 30 item Positive and Negative Symptoms Scale (PANSS) was developed to assess these symptoms in a quick and reliable manner together with a measure of General Psychopathology. The Positive and Negative scales consist of 7 items in each which are scored on a 7 point scale (1 = absent, 7 = severe). The General scale consists of 16 items, again rated on a 7 point scale. Scores for each scale can range from 7 – 49 for both the Positive and Negative scales and from 16 – 112 for the General scale. All items were derived from two established rating scales, namely the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) from which 18 items were selected, and the Psychopathology Rating Scale (PRS) (Singh & Kay, 1975a) from which 12 items were selected.

The PANSS incorporated a fourth scale, the Bipolar Composite subscale which can be calculated by subtracting the Negative subscale score from the Positive subscale score, providing a Bipolar index with scores ranging from -42 to +42. The PANSS is a reliable and sensitive measure which also has good construct and predictive validity. (Kay et al., 1987).

(d) Scale for the Assessment of Negative Symptoms

The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981) is a rating scale designed to assess 30 negative symptoms often observed in schizophrenia and incorporates five global symptoms (alogia, affective flattening, avolition-apathy, anhedonia and attentional impairment). Ratings are based on a 6 point scale from 0 to 5 (0 = no evidence, 5 = severe). Ratings are based on observations during a clinical interview as well as by the consideration of information from family members, nurses and ward staff. The SANS was designed to capture a time period of up to one month and is therefore a useful tool for measuring changes in clinical status in addition to providing an assessment of the severity of negative symptoms. The SANS provides several types of scores, each of which provides a measure of severity, including an overall global rating (by summing all 5 global symptoms scores), global ratings for individual negative symptom complexes which provides an index of the level of severity for each symptom. Sub-scale scores can also be calculated for each of the five global symptoms as well as calculating an overall score for the full 30 items. The SANS has been found to have good reliability as well as good validity and excellent interrater reliability (Andreasen, 1981).

(e) Global Assessment of Function

The severity of psychiatric illness can be scored using the Global Assessment of Functioning (GAF) (DSM-III-R, American Psychiatric Association, 1987) which was derived from an earlier rating scale - the Global Assessment Scale (GAS) (Endicott, Spitzer, & Fleiss, 1976). The GAF is known and used around the world and forms Axis V of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR). The GAF rates psychological, social, and occupational functioning and is intended to be a generic rating of how a patient is functioning overall, as oppose to a diagnosis-specific scoring system.

The GAF is a simple and quick scale to use and covers the full spectrum from severe psychopathology to no psychiatric symptoms. Scores can be either a single overall score from 1 to 100, or scores can be separated to reflect 'symptoms' (GAF-S) and 'functioning' (GAF-F), again with scores from 1 to 100 (Aas, 2011). In general, the GAF has been found to have good reliability and validity (Jones et al., 1995), however its' validity has been questioned due to the subjective nature of rating (Aas, 2011).

(f) Young Mania Rating Scale

The Young Mania Rating Scale (YMRS) (Young et al., 1978) was designed to assess the severity of mania, from mild to severe. Its design is based on the Hamilton Rating Scale for Depression (see below) and consists of eleven items which are rated by clinicians and during a clinical interview and are based on behavioural observations by the clinician, together with a subjective report from the patient on their condition over the previous 2 days. To compensate for poor co-operation in cases where patients are particularly ill, four questions (No's 5, 6, 8 and 9) are allocated additional weight. The Young Mania Rating Scale was considered necessary as previous rating scales were felt to be too long to administer and/or lacked the necessary scope and sensitivity required to accurately rate the severity of mania. Each of the eleven items has five grades, each of which defines a specific level of severity. Item choice was based on published descriptors of the core symptoms of the manic phase in bipolar affective disorder covering all stages of the illness, from mild to severe. The Young Mania Rating Scale has been found to have good reliability, validity and sensitivity (Young et al., 1978).

(g) Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression (Hamilton, 1960) was created specifically for use on patients already diagnosed as suffering from an affective depressive disorder. The rating scale is quick and simple to use, and offers a practical tool in the assessment of treatment effects.

The scale consists of 17 items (Depressed Mood, Guilt, Suicide, Insomnia (initial, middle, delayed), Work and Interests, Retardation, Agitation, Anxiety (Psychic, Somatic), Somatic (gastrointestinal, general, genital), Hypochondriasis, Insight and Loss of Weight. Each item is rated on either a five point scale (0 – 4) or a three point scale (0 – 2) to determine the severity of a depressive episode. The three point scale is used where the item is difficult or impossible to rate (No's 4, 5, 6, 9, 12, 13, 14, 16, 17). The Hamilton Rating Scale for Depression is the most widely used scale by clinicians to rate the severity of clinical depression (O'Hara et al., 1983) and it has been found to have good reliability and validity between clinician raters, as well as clinician/novice (trained undergraduate) raters (O'Hara et al., 1983).

3.2.2 Self-Report Questionnaire Measures

(a) Beck Depression Inventory

The Beck Depression Inventory was created to ascertain a quantitative measure of the severity of depression (Beck et al., 1960). The inventory consists of 21 categories of symptoms and attitudes that were clinically derived as a result of systematic observations by the author of the characteristic symptoms and attitudes of depressed patients. Each category has 4 or 5 statements that are graded by severity from 0 – 3 (0 = no symptoms, 3 = severe). Categories were developed to reflect a particular behavioural manifestation of depression and include mood, pessimism, sense of failure, lack of satisfaction, guilt, sense of punishment, self-hate, self-accusations, self-punitive wishes, crying, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, loss of libido. The Beck Depression Inventory has been found to have good reliability as well as a high degree of validity (Addington et al., 1992).

(b) Altman Self-Rating Mania Rating Scale

The presence of, and severity of manic symptoms can be assessed by the Altman Self-Rating Mania Rating Scale (ASRM) (Altman et al., 1997). The scale is quick to administer, consisting of 5 items, each of which has 5 statements which are rated from 0 – 4. Scores are summed and a cut-off point of 6 or higher is considered to indicate a high probability that manic or hypomanic symptoms are present. This assumption is based on a specificity rate of 87.3% and a sensitivity rating of 85.5%.

The ASRM significantly correlates with the Young Mania Rating Scale (YMRS) as well as the Clinician-Administered Rating Scale for Mania (CARS-M) (Altman et al., 1994) and is compatible with DSM-IV criteria (American Psychiatric Association, 1994). It can be used in both inpatient and outpatient settings and can also be used as a psycho-educational tool to assist patients to recognise and track their own symptoms.

(c) Eysenck Personality Questionnaire

This 90 item questionnaire was developed to ascertain the personality constructs of neuroticism (N), extroversion (E), psychoticism (P) and social desirability (L) (Eysenck and Eysenck, 1975). Personality measures of neuroticism, extroversion and psychoticism are predicted on a '*biologically based theory of personality*' (Barrett et al., 1998). Across cultures, social desirability is also believed to have the same degree of measurement similarity (Barrett et al., 1998). Psychometric scales for each construct are derived from forced choice 'yes' or 'no' answers to a number of statements e.g. "Are you a talkative person?" which are summed to give a total score for each personality measure. The questionnaire contains 21 statements for extroversion, 23 for neuroticism, 25 for psychoticism and 21 for social desirability. The Eysenck Personality Questionnaire (EPQ) has good reliability and validity.

(d) Temperament Evaluation of the Memphis, Pisa, Paris and San Diego Autoquestionnaire

This self-report questionnaire was developed over a number of years and was designed to measure affective temperaments in psychiatric patients as well as healthy volunteers. There are five temperament sub-scales, namely cyclothymic, depressive, irritable, hyperthymic and anxious.

The questionnaire comprises a total of 39 forced choice 'true' or 'false' statements with 12 statements making up the cyclothymic sub-scale, 8 statements each make up the depressive, irritable and hyperthymic sub-scales and the anxious sub-scale consists of 3 statements. The TEMPS-A has good reliability and validity (Akiskal & Mallya, 1986).

(e) Kings Schizotypy Questionnaire

The Kings Schizotypy Questionnaire (KSQ) was devised as part of an unpublished doctoral thesis by Maureen Bernadette Williams (1993): "The Psychometric Assessment of Schizotypal Personality". The questionnaire consists of 63 forced choice 'yes' or 'no' statements with 9 questions each accounting for seven sub-groups, namely recurrent illusions 1, social isolation, social anxiety, recurrent illusions 2, magical thinking, paranoid ideation and ideas of reference. These sub-groups can be further reduced to two main sub-groups providing a total for 'positive symptoms' and 'negative symptoms' and/or a total score can be used. The statements were based on DSM-III (American Psychiatric Association, 1980).

3.2.3 Neuropsychological Assessments and Procedure

Twenty-six family members (translocation carriers: N=13, non-carriers: N=13), fifty patients (schizophrenia: N=32, bipolar disorder: N=16) and forty-two healthy control participants completed neuropsychological assessment. Participants were administered standardised neuropsychological measures to assess pre-morbid intelligence (National Adult Reading Test, NART) and general intelligence (Wechsler Abbreviated Scale of Intelligence WASI). The Brief Assessment of Cognition in Schizophrenia (BACS) was also administered to assess a range of cognitive domains including verbal memory (list learning), working memory (digit sequencing task), processing speed (verbal fluency, token motor task, symbol coding), and executive function/reasoning and problem solving (tower test). Finally, participants were assessed using the Simple and Five-Choice Reaction Time measures from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Tests were administered in the same order (as above) to each participant. Full details of all neuropsychological tests used are detailed below in order of administration:

(a) Verbal Intelligence (Premorbid ability)

Intelligence is known to correlate highly with cognitive ability (O'carroll 1995), and has also been shown to deteriorate in schizophrenia and to a lesser extent in bipolar disorder (Mortimer 1997). The National Adult Reading Test (NART; Nelson, 1982; NART–R; (Nelson and Willison 1991) is widely used to estimate premorbid intellectual ability as a result of its' presumed measure of crystallised intelligence. Knowledge based on acquired learning is considered less vulnerable to the effects of cognitive decline than tests of fluid intelligence (Whyte, McIntosh et al. 2005).

Participants are required to read aloud 50 irregular words i.e. words which do not follow the usual grapheme-phoneme correspondences (e.g. chord, ache) (Coltheart et al., 1988) therefore participants are not able to correctly pronounce words they are not already familiar with. The total errors score (words pronounced incorrectly) is then used to calculate an estimate of premorbid intelligence (Bright, Jaldow et al. 2002).

(b) General Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI) is an abbreviated version of Wechsler's Adult Intelligence Scale (WAIS) (Wechsler 1955). The WASI provides an overall estimate of general intelligence (full-4 or full-2) as well as sub-group estimates of verbal and performance intelligence. Verbal intelligence is estimated from tasks of vocabulary and similarities in which participants are asked to provide word definitions and verbally explain how two words are related. Performance intelligence is estimated from tasks of block design and matrix reasoning in which participants are asked to use blocks to create pre-determined patterns and select the correct shape from a choice of five shapes to complete an incomplete puzzle. The WASI provides an IQ estimate using all 4 of these sub-tests (Full-4) however the WASI can be abbreviated further and provide an IQ estimate using only 2 of the sub-tests, namely vocabulary and matrix reasoning (Full-2).

(c) Verbal Memory, Working Memory, Processing Speed and Executive Function

The Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe, Harvey et al. 2004) was designed to measure treatment-related changes in cognition and includes brief assessments of four neurocognitive domains: verbal memory, working memory, processing speed and reasoning and problem solving/executive function, details of which are provided below:

(d) Verbal memory

Verbal memory is assessed by a list learning task which involves participants being read a list of 15 words after which they are asked to recall as many of the words as they can remember. This procedure is repeated 5 times. The outcome measure used is the total number of words correctly recalled per trial.

(e) Working memory

Working memory is assessed by using a digit sequencing task in which participants are read sets of numbers which start with 2 digits and increase in length to a maximum of 8 digits. The numbers are read in a random order and participants are asked to repeat the numbers back in order from the lowest number to the highest. The outcome measure used is the number of trials in which all sets of numbers were repeated in the correct order.

(f) Motor speed

Motor speed is assessed by using a token motor task in which participants are given 60 seconds to place as many tokens as possible into a container. In total there are 100 tokens which are split so that there are 50 tokens on the left of the container and 50 on the right. Participants must use their right and left hands simultaneously to pick up one token in each hand and place them into the container at the same time. The outcome measure used is the total number of tokens placed correctly into the container.

(g) Processing speed

Processing speed is assessed by the administration of three verbal fluency tasks, namely two letter fluency tasks and a category fluency task. The Controlled Oral Word Association Test is administered to assess letter fluency and is administered twice. Participants are asked to name as many words as they can think of that begin with a specific letter of the alphabet – in this study the letters 'F' and 'S' are used. For category instances (semantic fluency) participants are asked to name as many animals as they can think of in 60 seconds. The outcome measure used is the total number of words generated per trial.

(h) Attention and processing speed

Attention and processing speed is assessed by using a symbol coding task in which participants have 90 seconds in which to write in the numerals 1 – 9 on a response sheet as matches to symbols which appear in a key which is provided on the response sheet. The outcome measure used is the total number of correct responses.

(i) Executive function/reasoning and problem solving

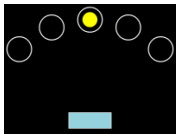
Executive function/reasoning and problem solving is assessed using the Tower of London task in which participants are asked to work out the least number of moves it would take to make one picture (Picture 'A') look like another picture (Picture 'B'). Both pictures are shown simultaneously and show 3 different coloured balls arranged on 3 pegs of differing heights. The tallest peg can hold all 3 balls, the middle peg can hold 2 balls and the smallest peg can only hold one ball.

This task employs the standard rules that apply to tower tests in that balls can only be moved one at a time and balls which are on top of other balls must be moved to an available space first (Keefe et al., 2008). The outcome measure used is the total number of correct responses.

(j) Reaction Time

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computer-based assessment system that uses a touch screen computer to administer a battery of neuropsychological tests designed to assess various cognitive functions (Sahakian, Morris et al. 1988).

(k) Psychomotor Co-ordination and Motor Speed



Simple Reaction Time measures each participant's response time when attending to a visual target where the stimulus is predictable. The Reaction Time Test (RTI) is able to separate response latency from movement time in both the simple and 5-choice stages. Participants are required to complete five stages which increase in complexity: in the single-choice stage participants must react as soon as they see a yellow dot appear on the screen and in the 5-choice stage the dot may appear in any one of five locations. Participants respond either by simply touching the screen or using a press-pad, and in the later stages they are required to do both. Outcome measures are divided into simple and 5-choice reaction time and simple and five-choice movement time.

3.3 Analysis

The primary contrasts of interest were the direct comparisons between members of the *t*(1;11) kindred with the translocation and those members of the family without the translocation, co-varying for demographic variables known to impact on neurocognitive measures, i.e. age, gender and (where relevant) general intelligence (IQ). Group effects were also of interest, specifically *t*(1;11) translocation carriers compared by diagnosis for impact of the *t*(1;11) translocation.

Raw test data were used in the analyses. Kolmogorov-Smirnov Z tests - using standardised residuals - confirmed all test distributions to be normal. Independent samples *t*-tests were used to conduct main group comparisons. Where data were found to violate assumptions of homogeneity of error variance, the equal variances *not* assumed statistic was used. Sub-group comparisons were subjected to a one-way analysis of variance (ANOVA) and a general linear model univariate analysis of covariance where appropriate. Measures of effect size are provided (Cohen's *d*) which have been calculated using the unadjusted means, standard deviations and sample sizes. Tests were two-tailed and statistical significance was considered at $p<0.05$. Pearson Product Moment Correlation Analysis were used to determine whether there were any relationships between neuropsychological, clinical, polygenic risk profile scores, antipsychotic medication (CPZ equivalents) and self-reported personality/mood data. Partial correlations were conducted to control for age, gender and current I.Q. (premorbid I.Q. when current I.Q. was the variable of interest).

For polygenic risk analyses, the number of variants scored in each participant was retained and used as a covariate in all analyses (CNT).

For all analyses, whether any differences between the groups were associated with psychopathology was investigated by examining the results for diagnostic sub-groups (psychotic disorder, recurrent depression, other diagnosis) of those with the translocation, as well as relating cognitive measures to the PANSS general, and positive psychotic symptom severity ratings in those with and without the *t*(1;11) translocation.

Due to the uniqueness of the *DISC1* kindred, opportunities to conduct investigations are very rare and therefore additional exploratory analyses were conducted which resulted in a relatively large number of assessments. To reduce the possibility of Type II errors, all significant *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

As a first step, data for *t*(1;11) carriers and non-carriers were directly compared without co-varying for any of the known demographic variables likely to impact on neurocognitive measures. The analyses were then repeated, co-varying for age, gender and current I.Q. to determine if there were any significant differences between translocation status and which of the demographic variables, if any, impact on these results. Where homogeneity of variance assumptions were violated, non-parametric analyses were conducted and reported.

A similar approach was taken in the analysis of the patient and control data to keep the analyses in line and to allow for a visual inspection of the results between *DISC1 t*(1;11) carriers and non-carriers and those from patients with schizophrenia and bipolar disorder, as the primary aim of recruiting these samples was to act as a 'positive' control group for the *DISC1* family. This provides an opportunity to establish robust effects of the *t*(1;11) translocation within the family, and to evaluate the possibly confounding effects of having a psychotic disorder.

Research into how similar family members' brains are anatomically has suggested that certain areas are highly heritable (Glahn et al., 2007b).

This means that direct comparisons between members of one family with a group of unrelated individuals would be significantly confounded by the shared heredity within the family. Therefore, direct comparisons between the *t*(1;11) kindred and patients or controls were not performed. The recruitment of the patient and control groups allows for the comparison of the effects of having a psychiatric disorder in general to the effects of the *t*(1;11) translocation within the family, without the need for direct comparisons between family members and patients.

3.3.1 Genotyping

As genotyping was performed elsewhere as part of a larger study - the 'Scottish Family Mental Health Study' (SFMHS) – genotyping methods are provided in Appendix 1.

3.3.2 Polygenic Risk Profile Scores

As above, polygenic risk profile scores were generated elsewhere as part of a larger study - 'the 'Scottish Family Mental Health Study' (SFMHS) therefore methods for polygenic risk profiling are provided in Appendix 2.

Chapter 4: Results – *DISC1 t*(1;11) Carriers and Non-Carriers

4. *DISC1 t*(1;11) Carriers and Non-Carriers

4.1 Demographic Details

Sample demographics, including clinical ratings for the *t*(1;11) family are detailed in table 4.1.

Table 4.1 - Sample Demographics

Sample Size (N=29)	**T/L Carriers (N=14)**	**Non-Carriers (N=15)**
Gender (M/F)	7/7	5/10
	Mean (SD)	***Mean (SD)***
Age	55.64 (15.28)	43.73 (20.19)
Premorbid IQ (NART)	103.07 (7.23)	104.54 (6.36)†
Current IQ (WASI)	88.15 (16.79)*	93.47(10.68)
Premorbid to Current IQ Difference	-15.38 (11.85)*	-13.31 (6.39)†
PANSS Total	46.86 (24.31)	33.73 (5.43)
PANSS Negative Symptoms	9.64 (9.06)	7.00 (0.00)
PANSS Positive Symptoms	10.14 (6.29)	7.00 (0.00)
PANSS General Symptoms	27.07 (10.73)	19.73 (5.43)
SANS	7.07 (26.46)	.40 (1.55)
GAF	75.14 (22.41)	85.67 (15.80)
YMRS	2.93 (5.40)	.00 (0.00)
HRSD	5.57 (6.21)	3.60 (6.16)
CPZ Equivalent**	600.00 (0.00)	0.00 (0.00)

*Table 4.1 – Sample demographics for DISC1 t(1;11) translocation carriers and non-carriers. * N=13, † N=13. Positive and Negative Symptoms Scale (PANSS); Scale for the Assessment of Negative Symptoms (SANS); Global Assessment of Function (GAF); Young Mania Rating Scale (YMRS); Hamilton Rating Scale for Depression (HRSD); Chlorpromazine Equivalent (CPZ). ** N=2*

4.1.1 Age, Gender, Premorbid IQ, Current IQ & IQ Difference

Initial group comparisons were conducted between all *t*(1;11) carriers (n=14) and non-carriers (n=15). Demographic variables of age (Figure 4.1), gender, premorbid IQ, current IQ and premorbid to current IQ difference (Table 4.1 and Figure 4.2) were compared using an independent samples *t*-test with group as a factor. All were found to be non-significant (p>.05) and were not controlled for in the preliminary analyses.

t(1;11) Carriers and Non-Carriers: Age

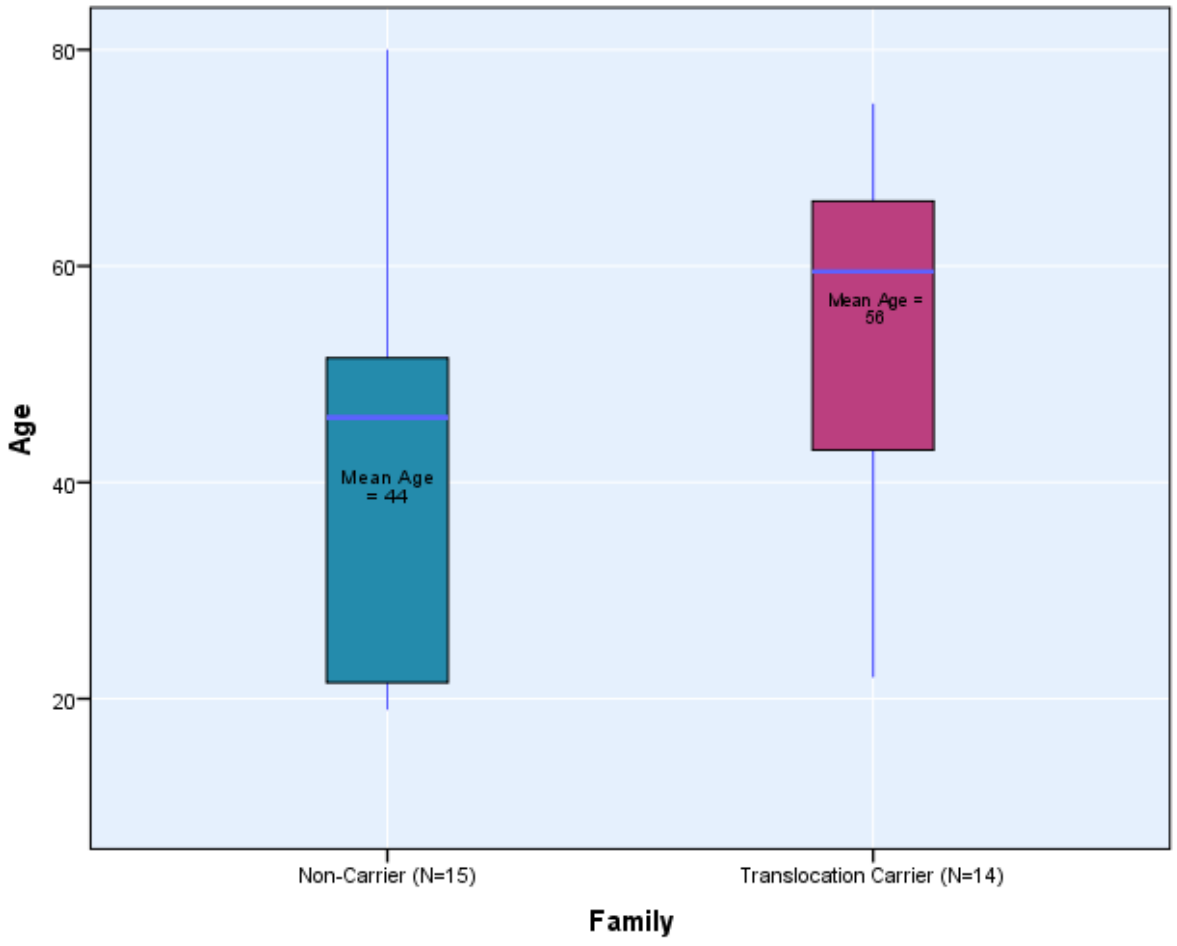


Figure 4.1 - Mean and median ages for DISC1 t(1;11) translocation carriers and non-carriers

t(1;11) Carriers and Non-Carriers: Premorbid I.Q., Current I.Q. and I.Q. Difference

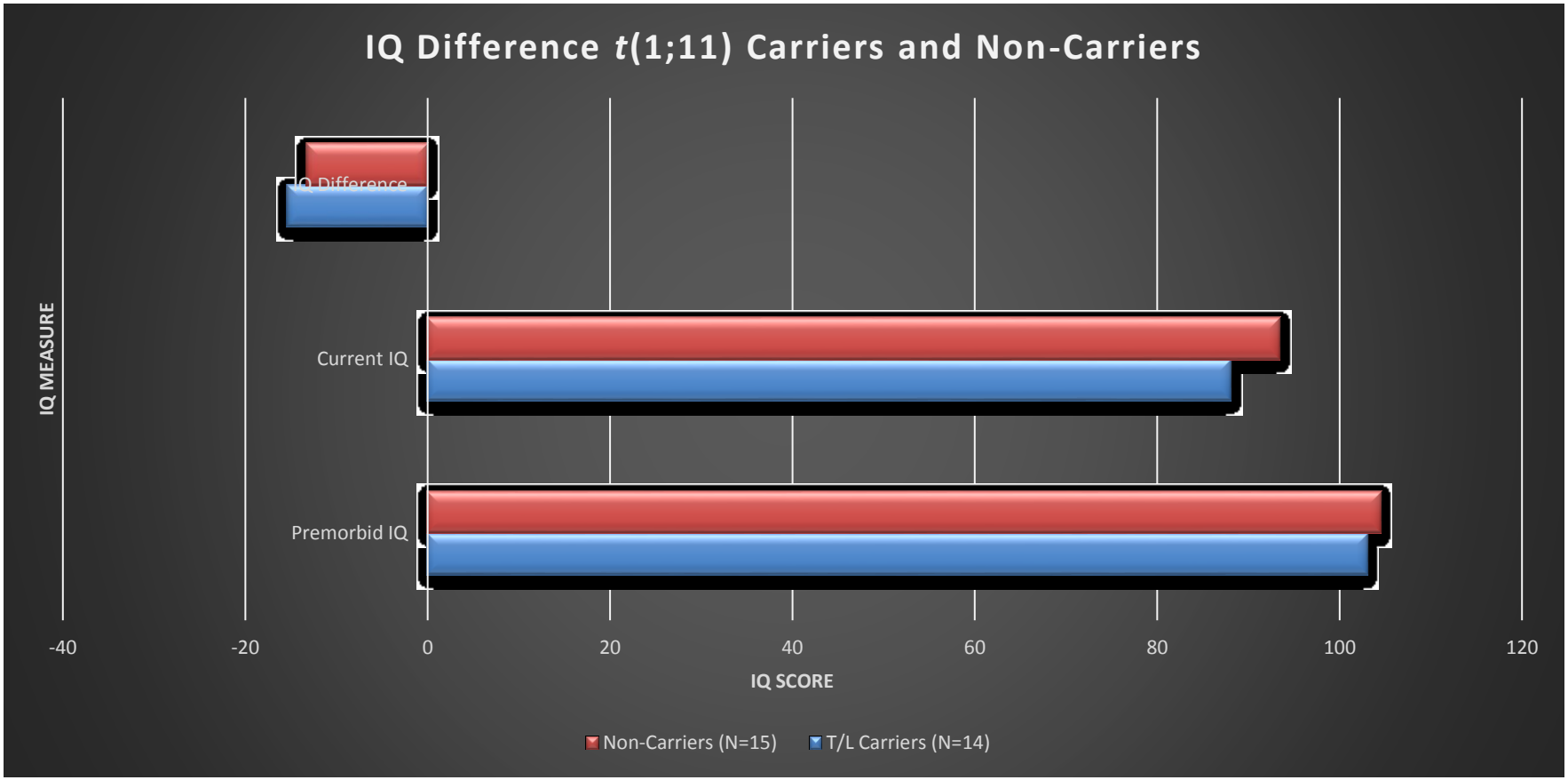


Figure 4.2 – Premorbid IQ, Current IQ and Premorbid to Current IQ Difference – DISC1 t(1;11) translocation carriers and non-carriers

4.1.2 Brief Assessment of Cognition in Schizophrenia (BACS)

An initial comparison of the performance data for the six assessments which make up the Brief Assessment of Cognition in Schizophrenia (BACS) did not identify any significant results between *t*(1;11) translocation carries (n=13) and non-carriers (n=13) (Figure 4.3). A general linear model univariate analysis of covariance (homogeneity of error variance met) was then conducted to control for age, gender and current IQ (all $p>.05$). There was, however, a moderate to large effect size (Cohen's $d = -0.8$) for attention and processing speed as measured by a symbol coding task (Figure 4.5).

Means and Standard Deviations for the raw data from *t*(1;11) carriers and non-carriers' performance for each of the tasks which make up the Brief Assessment of Cognition in Schizophrenia, together with both CANTAB reaction time tasks are provided in Table 4.2.

Statistical conclusion validity is concerned with ensuring that any reported relationships between variables are reasonable and correct. It may be the case here that there are, in fact, some significant relationships between translocation status and specific cognitive domains as evidenced by the moderate to large effect sizes seen for motor speed and attention and processing speed (see Figure 4.5). Significant relationships may not have been detected due to insufficient power. Low statistical power can lead to a higher probability of committing a Type II error and concluding that there is no effect when there actually is (Cohen, J. 1992). It is encouraging, none the less, that strong associations have been identified which can be investigated further in future work.

t(1;11) Carriers and Non-Carriers - Means and Standard Deviations:

Brief Assessment of Cognition in Schizophrenia (BACS) / CANTAB Reaction Times Tasks

COGNITIVE DOMAIN/ BACS/CANTAB TASK	**TRANSLOCATION CARRIERS RAW DATA (N=13)**	**NON-CARRIERS RAW DATA (N=13)**
	Mean (Standard Deviation)	Mean (Standard Deviation)
VERBAL MEMORY: (LIST LEARNING TASK)	35.46 (14.69)	40.85 (13.71)
WORKING MEMORY: (DIGIT SEQUENCING TASK)	15.00 (9.57)	17.62 (6.54)
MOTOR SPEED: (TOKEN MOTOR TASK)	70.77 (27.14)	79.62 (13.85)
PROCESSING SPEED: (VERBAL FLUENCY TASK)	41.15 (20.87)	48.15 (13.39)
ATTENTION & PROCESSING SPEED: (SYMBOL CODING TASK)	35.92 (24.07)	50.31 (11.03)
EXECUTIVE FUNCTION: (TOWER OF LONDON TASK)	11.77 (8.52)	13.92 (2.87)
SIMPLE REACTION TIME (CANTAB)	481.27 (210.54)	347.60 (83.95)
FIVE-CHOICE REACTION TIME (CANTAB)	507.77 (243.98)	362.08 (69.93)

Table 4.2 – Brief Assessment of Cognition in Schizophrenia (BACS) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Means and Standard Deviations for DISC1 t(1;11) (N=26) Translocation Carriers (N=13) and Non-Carriers (N=13)

t(1;11) Carriers and Non-Carriers: Brief Assessment of Cognition in Schizophrenia (BACS) Test Battery

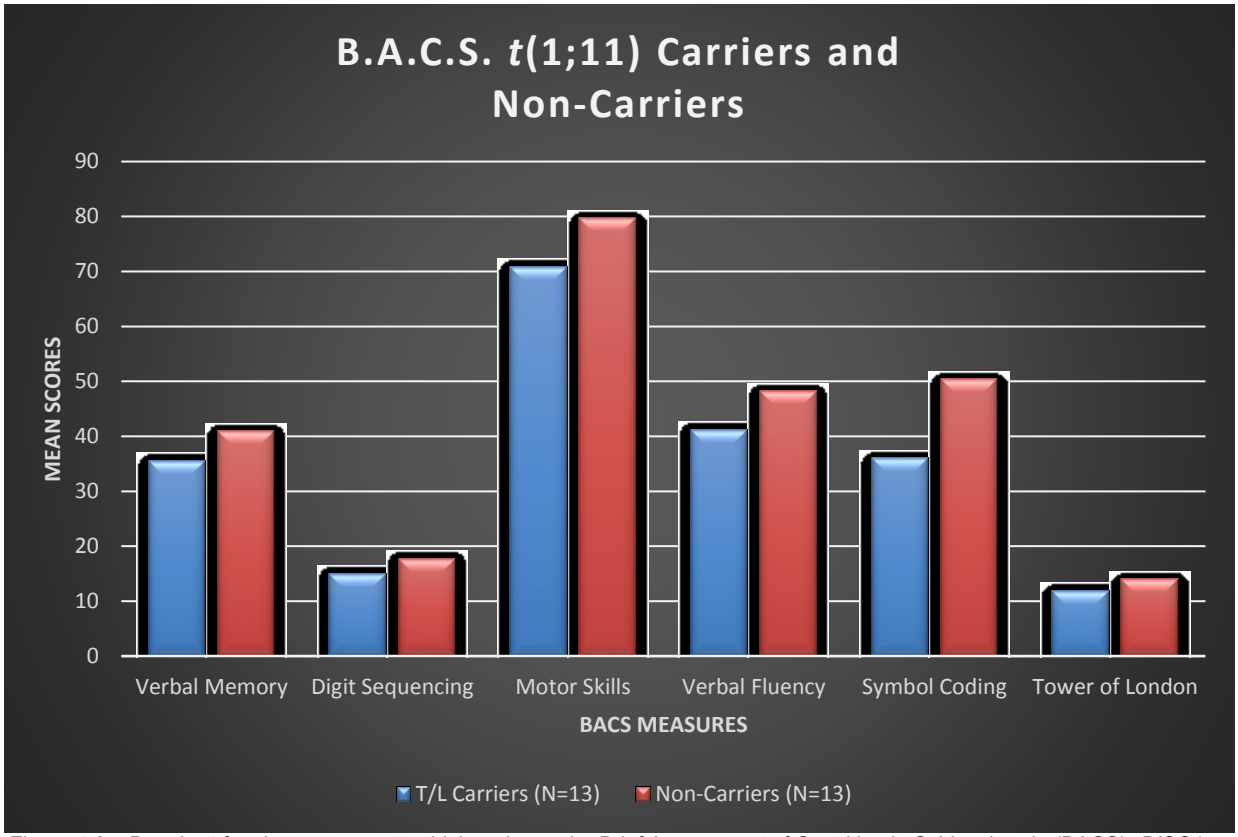


Figure 4.3 – Bar chart for six assessments which make up the Brief Assessment of Cognition in Schizophrenia (BACS): *DISC1* *t*(1;11) Translocation Carriers and Non-Carriers.

4.1.3 Cambridge Neuropsychological Test Automated Battery (CANTAB)

An initial main group analysis was conducted between *t*(1;11) carriers (n=13) and non-carriers (n=13) on the performance data from two CANTAB assessments to measure reaction time using an independent samples *t*-test with group as a factor. Mean scores (Table 4.2) met the significance threshold (p≤.05) for simple reaction time (equal variances *not* assumed) (*t* = -2.126, df = 15.722, ***p* = *.050***) and five-choice reaction time (equal variances assumed) (*t* = -2.070, df = 24, ***p* = *.049***) (Figure 4.4), both of which also produced moderate to large effect sizes (Cohen's *d* = 0.87 and 0.84 respectively) (Figure 4.5).

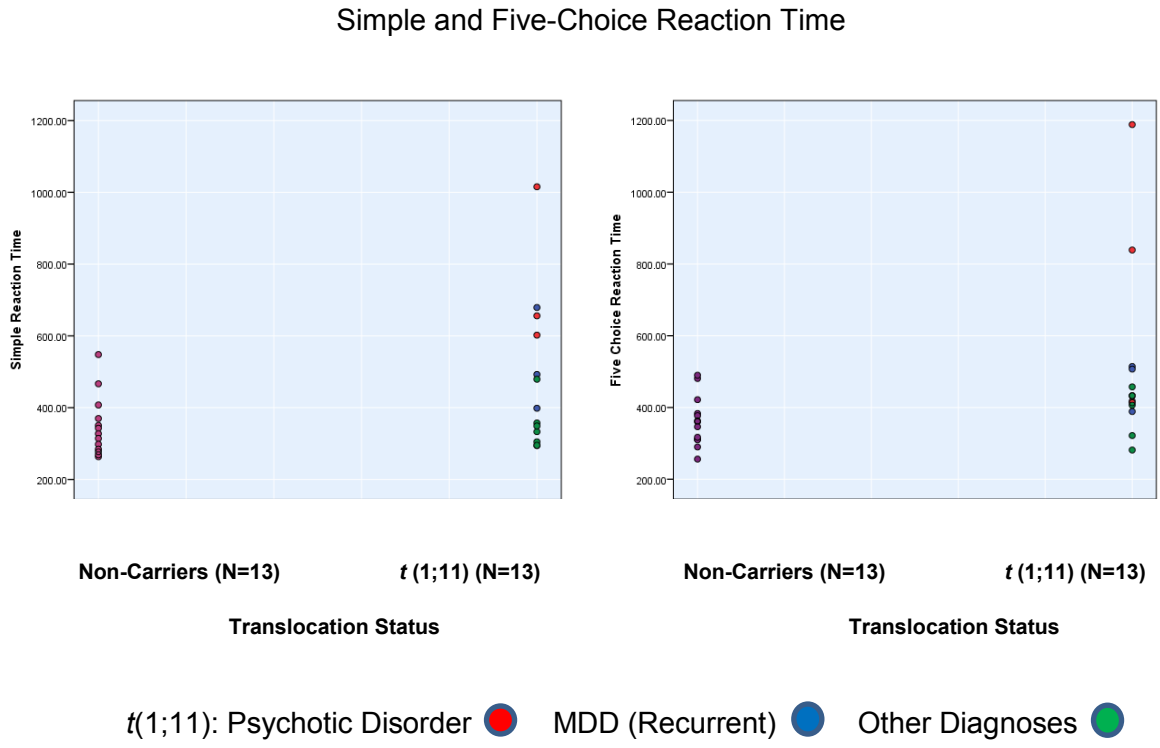


Figure 4.4 – Scatterplots for Simple and Five-Choice Reaction Time between DISC1 t(1;11) Translocation Carriers and Non-Carriers.

A general linear model univariate analysis of covariance (homogeneity of error variance met) was then conducted to control for current IQ, with results remaining significant - simple reaction time (*F*(1,23) 4.948, ***p* = *.036***); five-choice reaction time (*F*(1,23) 4.791, ***p* = *.039***). Results were not robust, however, to control for age, gender and current IQ (*p* = > 0.5 for both).

Visual inspection of the scatterplots for simple and five-choice reaction time (Figure 4.4) suggest that a degree of difference may be contributed to by outliers. This is an important consideration as two of the three *t*(1;11) carriers in the 'Psychotic Disorder' sub-group were receiving antipsychotic medication. Extrapyramidal symptoms of antipsychotic medication can have a powerful effect on fine motor function which is required to perform these tasks (Owens, D.C. 2014). To account for this possibility the outlier from the 'Psychotic Disorder' sub-group was removed and the analyses were repeated. Five-Choice Reaction Time was robust controlling for age, gender and current IQ (***p*=.040**) however Simple Reaction Time marginally failed to reach significance (p=.051).

Effect Sizes for Neuropsychological Measures between *DISC1 t*(1;11) Translocation Carriers and Non-Carriers

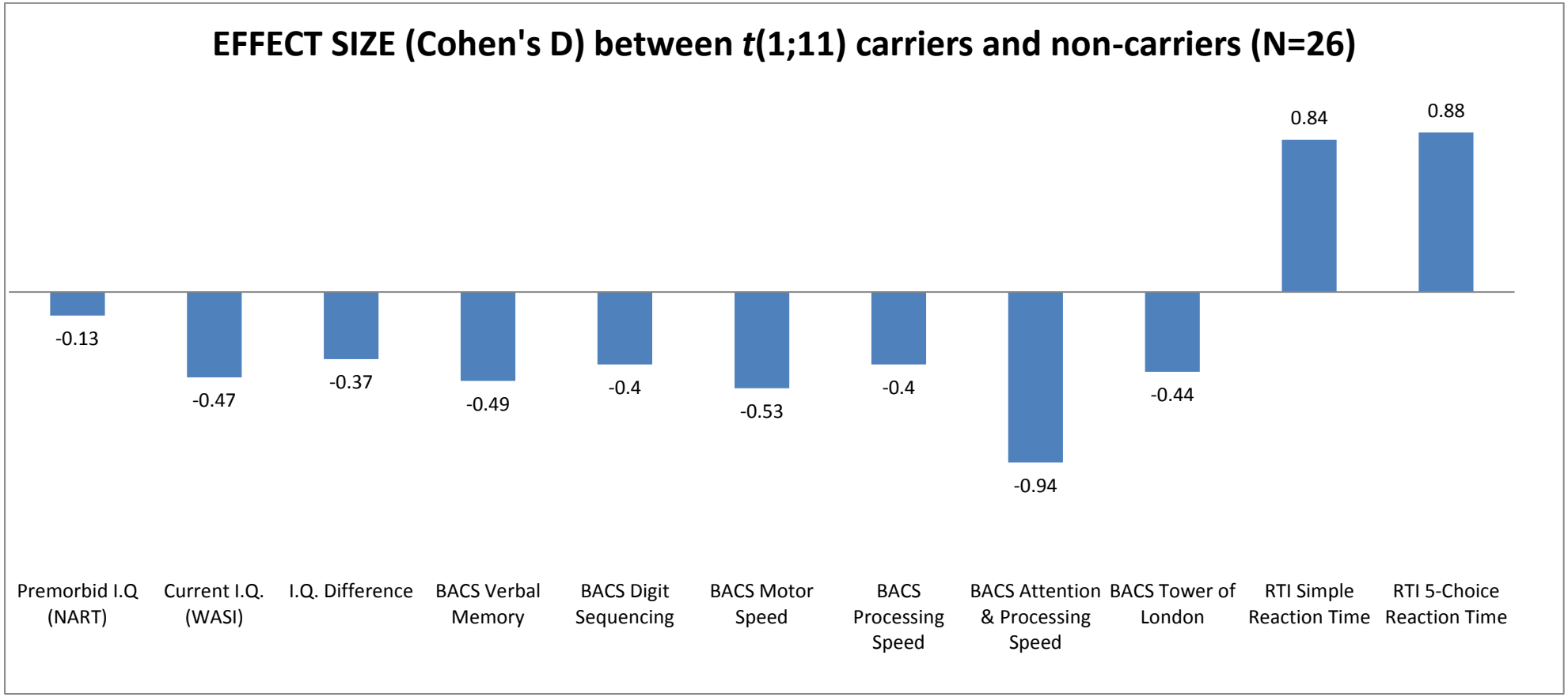


Figure 4.5 - Effect sizes for all neuropsychological measures

4.2 Clinical Symptom Rating Scales: *DISC1* Carriers and Non-Carriers

In line with the main hypotheses, symptom severity rating scales were investigated within the *t*(1;11) kindred with the additional hypotheses that IQ and processing speed tasks would be significantly associated with measures from the Positive and Negative Symptoms Scale (PANSS) - particularly positive symptoms. As this offered a rare opportunity to investigate the *t*(1;11) kindred, additional exploratory analyses were also conducted, including examining self-reported measures of personality and mood.

Symptom severity rating scales were compared between all *t*(1;11) carriers and non-carriers using independent samples *t*-tests. A significant difference was identified between translocation status and the sub-group measuring 'general symptoms' from the Positive and Negative Symptoms Scale (PANSS) ($t = 2.35$, df = 27, $\boldsymbol{p = .026}$) (equal variances assumed). This result became non-significant after controlling for age and gender using a general linear model univariate analysis of covariance.

4.3 Clinical Symptom Rating Scales and Neuropsychological Assessments: *DISC1* Carriers and Non-Carriers as a Group

Pearson bivariate correlational analyses were conducted between clinical ratings of symptom severity and neuropsychological assessments with the *t*(1;11) kindred (N=26). Current IQ, simple and/or five-choice reaction time and motor speed were of particular interest and were all found to be significantly associated with measures from the Positive and Negative Symptoms Scale (PANSS) as well as the Scale for the Assessment of Negative Symptoms (SANS). Pearson partial correlational analyses were conducted to control for age, gender and current IQ (premorbid IQ where current IQ was the variable of interest) and *p* values were corrected using the FDR procedure in which the majority of results remained significant (Table 4.3).

t(1;11) Carriers and Non-Carriers: Correlational Analysis - Neuropsychological Assessments/Clinical Measures

	Simple Reaction Time	Five-Choice Reaction Time	Current IQ	Motor Speed
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
PANSS Total	***r = .71 (p = <.001)***	***r = .84 (p = <.001)***	***r = -.56 (p = .006)***	***r = -.63 (p = .001)***
PANSS Positive	***r = .53 (p = .010)***	***r = .75 (p = <.001)***	***r = -.55 (p = .007)***	***r = -.49 (p = .018)***
PANSS Negative	***r = .61 (p = .002)***	***r = .70 (p = <.001)***	*r = -.34 (p = .117)*	***r = -.67 (p = <.001)***
PANSS General	***r = .66 (p = .001)***	***r = .73 (p = <.001)***	***r = -.60 (p = .003)***	***r = -.48 (p = .019)***
SANS	***r = .64 (p = .001)***	***r = .71 (p = <.001)***	*r* = -.32 (*p* = .135)	***r = -.67 (p = <.001)***

Table 4.3 – Correlational Analysis: Neuropsychological Assessments/Clinical Measures: *DISC1 t*(1;11) Translocation Carriers and Non-Carriers (N=26)

- *p*-values have been controlled for age, gender and current IQ (premorbid IQ where current IQ is the variable of interest). For all correlations, *p* values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

4.4 Polygenic Risk Profile Scores: *DISC1* Carriers and Non-Carriers

As *DISC1* was originally identified as a direct result of this kindred and is primarily thought to increase risk for schizophrenia, we also examined the effects of polygenic risk for schizophrenia given that the *t*(1;11) translocation is not always associated with illness, let alone schizophrenia, and PGRSs is a risk factor for schizophrenia, bipolar disorder and depression that may interact with translocation status to influence diagnosis. It was hypothesised that polygenic risk for schizophrenia would be significantly associated with current IQ and/or measures of processing speed and also with positive symptomology within the family and especially within *t*(1;11) carriers.

Initial comparisons between translocation carriers and non-carriers using independent samples *t*-tests did not identify any significant differences between the polygenic risk profile scores for schizophrenia (p>.05) or major depressive disorder (p>.05) within the family (Table 4.4). There was, however, a significant difference between family carriers and non-carriers for polygenic risk for bipolar disorder (t = -2.202, df = 27, ***p = 0.036***) (equal variances assumed) (Table 4.4 and Figure 4.6). This result remained significant using a general linear model univariate analysis of covariance (homogeneity of error variance met) to control for CNT (F(1,27) 4.847, ***p = 0.036***).

Polygenic Risk Profile Score		N	Mean	Std. Deviation
SCZ Score	T/L Carrier	N=14	.000007929	.0000243226
	Non-Carrier	N=15	.000003400	.0000276637
BP Score	T/L Carrier	N=14	.000006914	.0000354206
	Non-Carrier	N=15	-.000024607	.0000412033
MDD Score	T/L Carrier	N=14	.000004957	.0000262889
	Non-Carrier	N=15	-.000000693	.0000411534

Table 4.4 - Polygenic Risk Profile Scores: DISC1 t(1;11) Translocation Carriers and Non-Carriers (N=29)

t(1;11) Carriers and Non-Carriers: Polygenic Risk for Bipolar Disorder

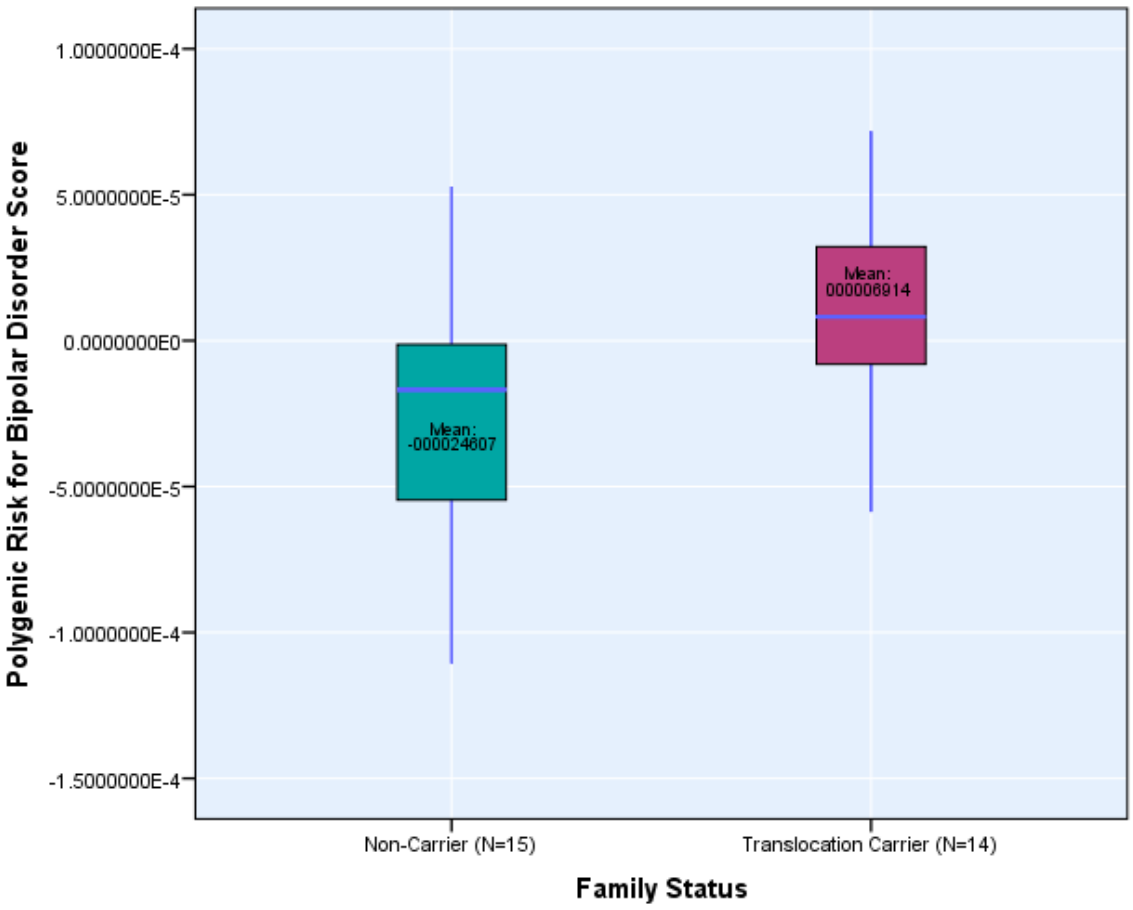


Figure 4.6 – Polygenic Risk for Bipolar Disorder: DISC1 t(1;11) Translocation Carriers and Non-Carriers

4.4.1 Polygenic Risk Profile Scores, Neuropsychology and Clinical Symptoms: *DISC1 t*(1;11) Carriers and Non-Carriers as a Group

No significant associations were identified between any of the polygenic risk profile scores and any of the neuropsychological measures (all p>.05) however as polygenic risk for schizophrenia was of particular interest - especially regarding neurocognitive function - it is worth noting that a weak association was identified between polygenic risk for schizophrenia and simple reaction time which marginally missed significance (r = .38, p = 0.052) (Table 4.5).

For clinical measures, polygenic risk for schizophrenia was significantly associated with two sub-groups from the Positive and Negative Symptom Scale (PANSS), namely PANSS 'total score' (***r = .37, p = 0.048***) and PANSS 'general symptoms' (***r = .42, p = 0.025***) (Table 4.5). These results became non-significant after correcting using the FDR procedure and controlling for CNT (Table 4.6).

No significant associations were identified between polygenic risk for either bipolar disorder or major depressive disorder with any of the clinical rating scales (all p>.05).

	Simple Reaction Time*	PANSS Total Score	PANSS General Symptoms
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
Polygenic Risk for Schizophrenia	*r* = .38 (*p* = .052)	*r* = .37 **(*p* = .048)**	*r* = .42 **(*p* = .025)**

*Table 4.5 – Correlational Analysis Results – Polygenic Risk for Schizophrenia – DISC1 t(1;11) Translocation Carriers and Non-Carriers (N=29) *(N=26)*

Controlling for CNT	Simple Reaction Time*	PANSS Total Score	PANSS General Symptoms
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
Polygenic Risk for Schizophrenia	*r* = .39 (*p* = .056)	*r* = .32 (*p* = .093)	*r* = .37 (*p* = .054)

*Table 4.6 – Correlational Analysis Results (Controlling for CNT) – Polygenic Risk for Schizophrenia – DISC1 t(1;11) Translocation Carriers and Non-Carriers (N=29) *(N=26)*

For all correlations, *p* values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

4.4.2 Self-Reported Measures of Personality and Mood: *DISC1 t*(1;11) Carriers and Non-Carriers

As the self-report questionnaire data was found to deviate from normality, non-parametric Mann-Whitney U analyses were conducted between *t*(1;11) carriers and non-carriers. A significant difference was identified between the self-reported measure of 'Anxiety' as measured by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-Questionnaire (TEMPS-A) (*U = 0.18*, ***p* = .015**) (exact significance result reported). No other significant differences were identified between these family members.

4.5 *DISC1 t*(1;11) Carriers by Sub-Group Diagnoses: Premorbid I.Q., Current I.Q. and I.Q. Difference

As per previous work by St. Clair et al., (1990) and Blackwood et al., (2001), thirteen *t*(1;11) carriers were sub-grouped according to diagnoses as follows: 'psychotic disorder' (n=3), 'major depressive disorder (recurrent)' (n=3), 'other diagnoses' (n=7).

4.5.1 Premorbid I.Q., Current I.Q. and I.Q. Difference; *DISC1 t*(1;11) Carriers by Sub-Group Diagnoses

An initial one-way analysis of variance (ANOVA) revealed significant differences ($p<.05$) in current IQ ($F(2,10)$ 6.343 ***p=.017***) and IQ difference (i.e. the difference between pre-morbid IQ scores and current IQ scores) ($F(2,10)$ 5.911 ***p=.020***). Pairwise comparisons later identified current IQ as being significantly lower in family members with 'psychotic disorder' compared to those with 'other diagnoses' (***p=.016***). IQ difference was also significantly greater in those with 'psychotic disorder' compared to those with 'other diagnoses' (***p=.019***). A general linear model univariate analysis of covariance (homogeneity of error variance met) was then used to control for age and gender which remained significant for current IQ ($F(2,8)$ 7.113 ***p=.017***) and IQ difference ($F(2,8)$ 6.452 ***p=.021***) (Table 4.7 and Figure 4.7).

IQ for *DISC1 t*(1;11) Translocation Carriers by Sub-Group Diagnoses

IQ Measure	*t*(1;11) Psychotic Disorder (N=3)	*t*(1;11) MDD(R) (N=3)	*t*(1;11) Other Diagnosis (N=7)	ANCOVA (Between Groups) Controlled for Age and Gender
	M (SD)	***M (SD)***	***M (SD)***	***'F' Sig***
Premorbid IQ	96.05 (3.99)	105.53 (4.13)	104.78 (2.49)	-
Current IQ	***67.21**** (6.32)	92.59 (6.59)	***95.230**** (4.25)	$F(2,8)$ 7.113, ***p = .017***
IQ Difference	***-29.14**** (4.38)	-13.05 (4.56)	***-10.49**** (2.94)	$F(2,8)$ 6.452 ***p = .021***

*Table 4.7 * Post-hoc analysis revealed significant between-group differences between 'Psychotic Disorder' and 'Other Diagnosis' controlling for age and gender*

t(1;11) Sub-Groups: Premorbid I.Q., Current I.Q. and I.Q. Difference

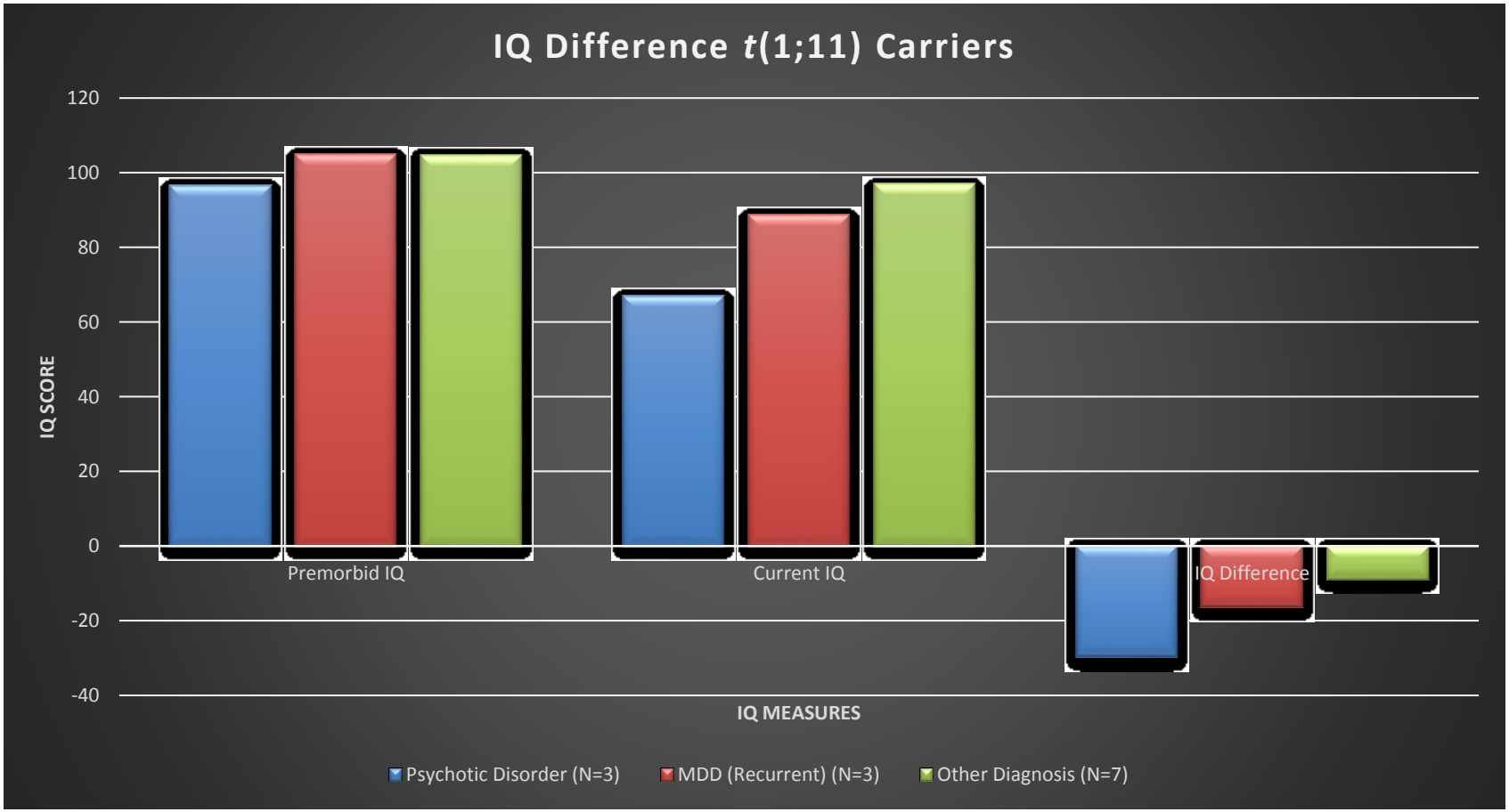


Figure 4.7 – Premorbid IQ, Current IQ and IQ Difference for DISC1 t(1;11) Translocation Carriers by Sub-Group Diagnoses

4.5.2 Brief Assessment of Cognition in Schizophrenia (BACS): *DISC1 t*(1;11) Carriers by Sub-Group Diagnoses

Initial comparison of the *t*(1;11) carriers' performance results from the six BACS assessments split by sub-group diagnoses revealed significantly reduced scores ($p<.05$) for verbal memory - as assessed by a list learning task ($F(2,10)$ 8.264 ***p=.008***), motor speed – as assessed by a token motor task ($F(2,10)$ 4.620 ***p=.038***) and attention and processing speed - as assessed by a symbol coding task ($F(2,10)$ 6.921 ***p=.013***) (Figure 4.8).

A general linear model univariate analysis of covariance (homogeneity of error variance met) was then used to control for age, gender and current IQ. Attention and processing speed remained significant ($F(2,7)$ 5.211 ***p=.041***) (Figure 4.9).

Means and Standard Deviations for the raw scores for the performances for each of the tasks which make up the Brief Assessment of Cognition in Schizophrenia, together with both CANTAB reaction time tasks for *t*(1;11) carriers by sub-group diagnoses are provided in Table 4.8).

t(1;11) Carriers by Sub-Group Diagnoses - Means and Standard Deviations:

Brief Assessment of Cognition in Schizophrenia (BACS) / CANTAB Reaction Times Tasks

COGNITIVE DOMAIN: BACS/CANTAB TASK	**T(1;11) PSYCHOTIC DISORDER RAW DATA (N=3)**	**T(1;11) MAJOR DEPRESSION RAW DATA (N=3)**	**T(1;11) OTHER DIAGNOSIS RAW DATA (N=7)**
	Mean (SD)	Mean (SD)	Mean (SD)
VERBAL MEMORY: (LIST LEARNING TASK)	15.33 (14.57)	38.67 (7.37)	42.71 (8.60)
WORKING MEMORY: (DIGIT SEQUENCING TASK)	6.00 (5.57)	16.67 (11.15)	18.14 (8.84)
MOTOR SPEED: (TOKEN MOTOR TASK)	39.33 (34.77)	70.67 (18.58)	84.29 (15.72)
PROCESSING SPEED: (VERBAL FLUENCY TASK)	22.67 (19.73)	35.67 (21.03)	51.43 (16.87)
ATTENTION & PROCESSING SPEED: (SYMBOL CODING TASK)	11.00 (12.77)	24.00 (21.17)	51.71 (16.80)
EXECUTIVE FUNCTION: (TOWER OF LONDON TASK)	5.67 (9.81)	12.33 (10.79)	14.14 (6.99)
SIMPLE REACTION TIME (CANTAB)	757.79 (224.69)	502.44 (166.21)	353.69 (71.91)
FIVE-CHOICE REACTION TIME (CANTAB)	811.32 (381.83)	447.66 (109.10)	403.45 (57.77)

Table 4.8 – Brief Assessment of Cognition in Schizophrenia (BACS) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Means and Standard Deviations for DISC1 t(1;11) (N=13) Translocation Carriers by Sub-Group Diagnosis: Psychotic Disorder (N=3), Major Depressive Disorder (N=3) and Other Diagnosis (N=7)

t(1;11) Sub-Groups: Brief Assessment of Cognition in Schizophrenia (BACS) Tasks

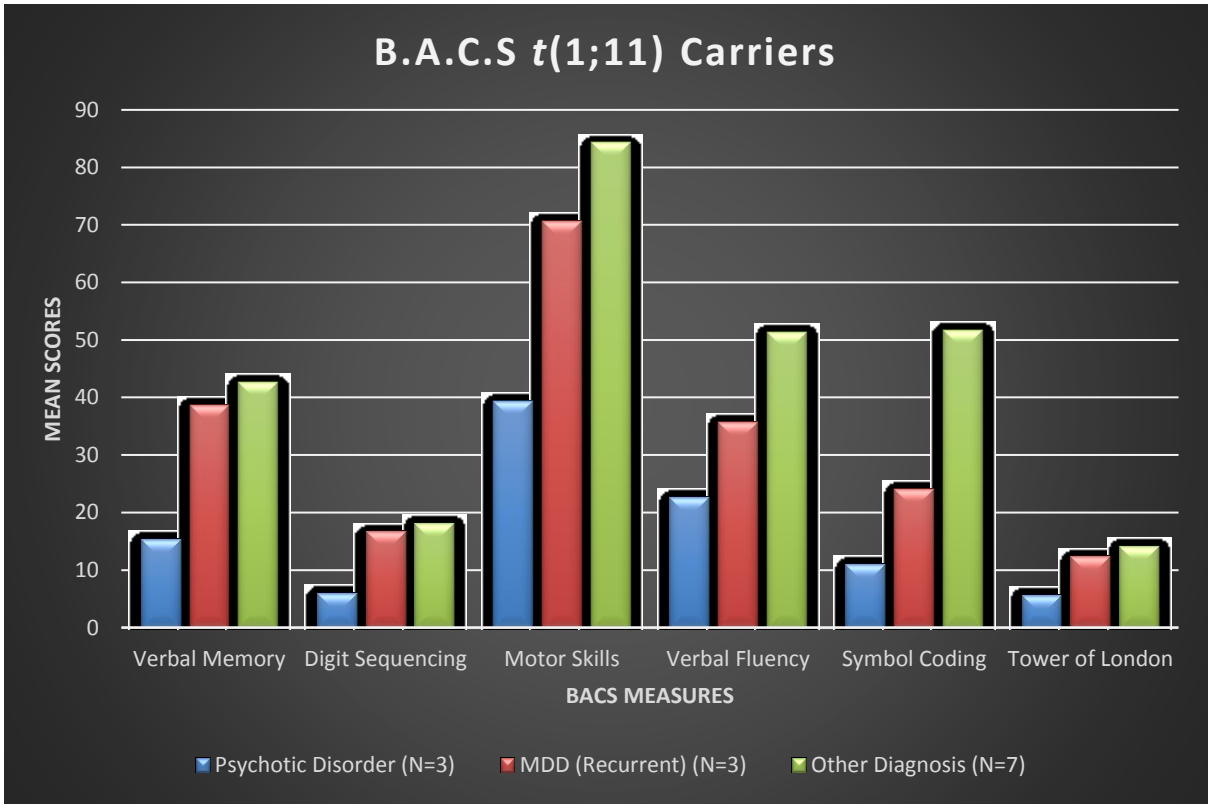


Figure 4.8 – Brief Assessment of Cognition in Schizophrenia (BACS) Measures for DISC1 t(1;11) Translocation Carriers by Sub-Group Diagnoses

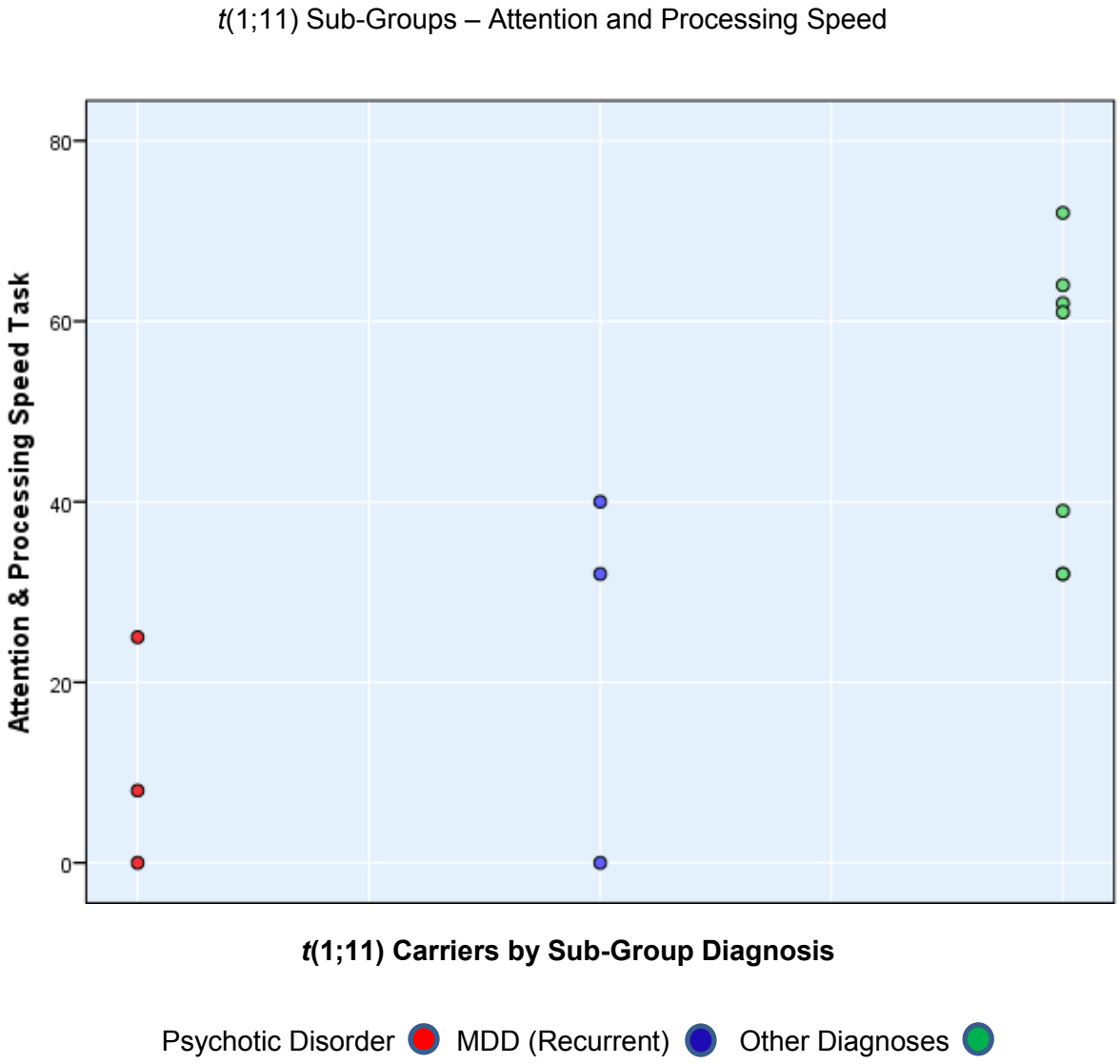


Figure 4.9 – Scatterplot for Attention and Processing Speed: DISC1 t(1;11) Translocation Carriers by Sub-Group Diagnoses

4.5.3 Cambridge Neuropsychological Test Automated Battery (CANTAB): *DISC1 t*(1;11) Carriers by Sub-Group Diagnoses

Performances by *DISC1 t*(1;11) carriers split by sub-group diagnoses were also compared on two CANTAB reaction time tasks using a one-way analysis of variance (see Table 4.8 for raw scores means/standard deviations). A significant between-groups difference was identified for simple reaction time (***p* > .05**). Multiple comparison post hoc analysis identified a significantly reduced performance between family members with 'psychotic disorder' and those with 'other diagnoses'. This result was not robust, however, controlling for age, gender and current IQ when using a general linear model univariate analysis of covariance (homogeneity of error variance met) (Figure 4.10).

Analysis of the five-choice reaction time task between *DISC1 t*(1;11) carriers by sub-group diagnoses was also non-significant (p>.05).

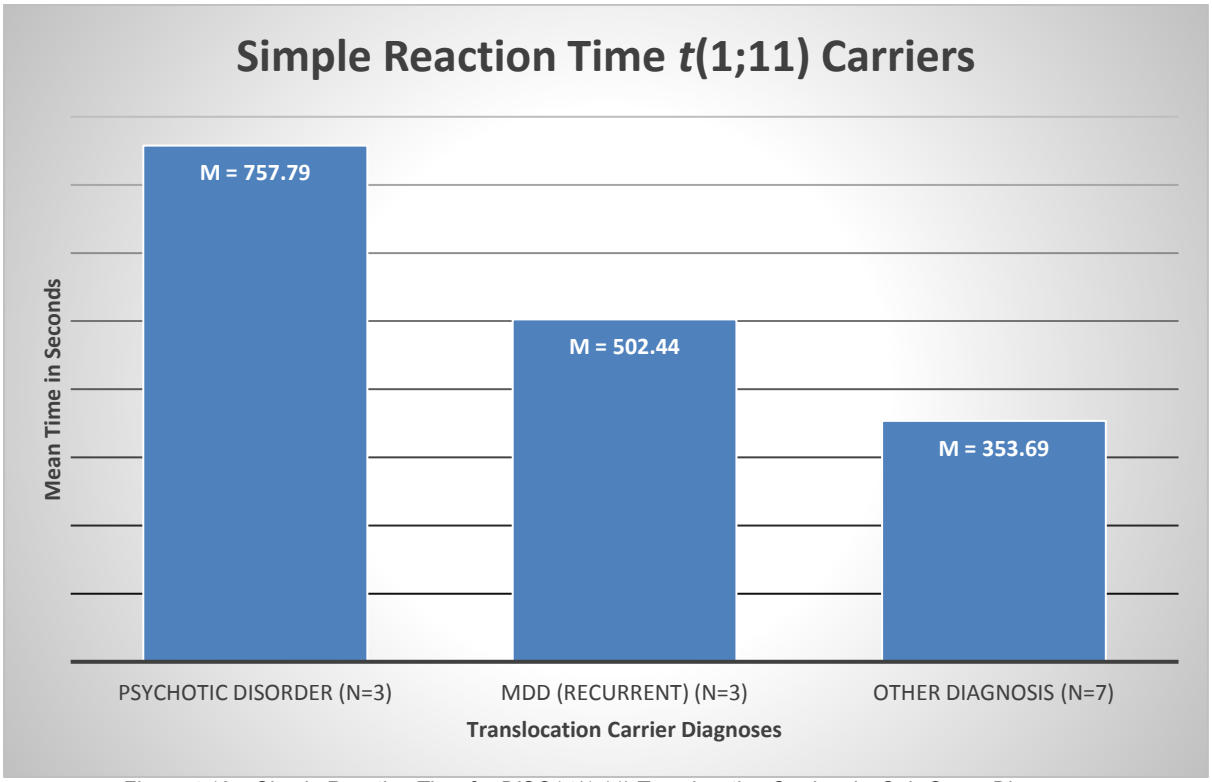


Figure 4.10 – Simple Reaction Time for DISC1 t(1;11) Translocation Carriers by Sub-Group Diagnoses

4.6 Clinical Symptom Rating Scales: *DISC1 t*(1;11) Carriers by Sub-Group Diagnoses

Initially, a one-way analysis of variance was conducted between symptom severity rating scales and *t*(1;11) translocation carriers split by diagnostic sub-group, revealing significant between-group differences for 'positive symptoms' from the PANSS; overall functioning as assessed by the GAF and the Hamilton Rating Scale for Depression. These results remained significant after controlling for age and gender using a general linear model univariate analysis of covariance (***p* = .041, *p* = .046 and *p* = .008** respectively). As expected, *t*(1;11) carriers with 'psychotic disorder' had greater symptom severity than those with 'other diagnoses' and similarly, carriers with 'major depressive disorder' also had greater symptom severity than those with 'other diagnoses'. As the homogeneity of variance assumption was found to be violated in the 'depression' rating, a non-parametric Kruskal-Wallis H test was also conducted in which 'depression' - as assessed by the Hamilton Rating Scale for Depression (HDRS) remained significant (***X²(2) = 9.91, p = .007***) (Figure 4.11).

t(1;11) Sub-Groups: Hamilton Depression Rating Scale

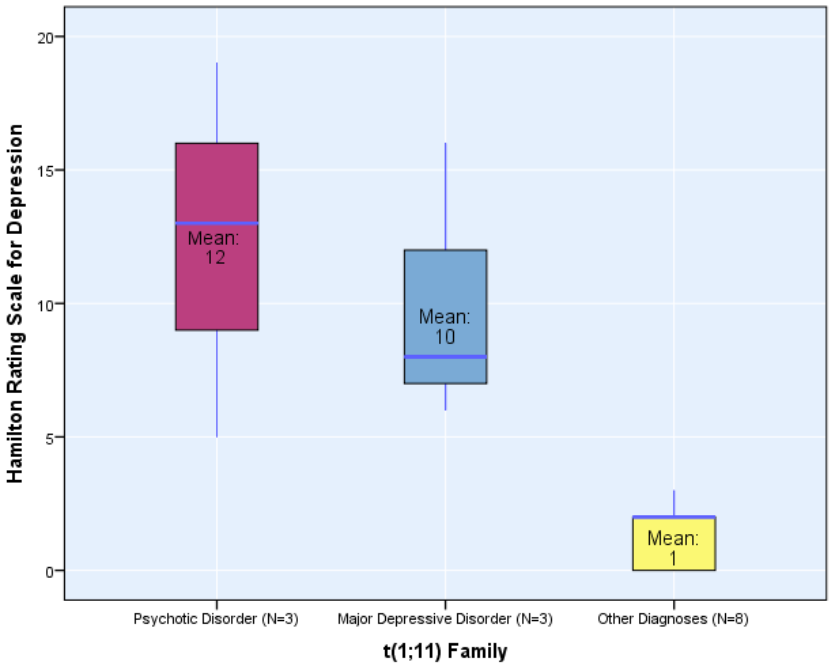


Figure 4.11 – Hamilton Rating Scale for Depression/DISC1 t(1;11) Translocation Carriers by Sub-Group Diagnoses

4.6.1 Clinical Symptom Rating Scales and Neuropsychological Assessments: *DISC1 t*(1;11) Carriers as a Group

Analyses were conducted between symptom severity rating scales and neuropsychological assessments for *t*(1;11) carriers (N=13). In line with the main hypotheses, IQ and measures of processing speed were hypothesised to be significantly associated with symptom severity, in particular positive symptomology. Current IQ, simple and/or five-choice reaction time and motor speed were of particular interest and as with the results for the family as a whole, these variables were also found to be significantly associated with measures from the Positive and Negative Symptoms Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS).

Pearson partial correlational analyses were conducted to control for age, gender and current IQ (premorbid IQ when current IQ was the variable of interest) at which point the previously significant results for simple reaction time were lost, however significant associations remained between three of the variables of interest and measures from the PANSS ('total score', 'positive symptoms' 'negative symptoms' and/or 'general symptoms') and the Scale for the Assessment of Negative Symptoms (SANS). Not all associations were robust, however, after correcting using the FDR procedure (Table 4.9).

	Five-Choice Reaction Time	Current IQ	Motor Speed
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
PANSS Total	***r = .89 (p = .001)***	***r = -.72 (p = .018)***	*r* = -.64 (*p* = .045)
PANSS Positive	*r* = .63 (*p* = .048)	*r* = -.70 (*p* = .023)	*r* = -.25 (*p* = .488)
PANSS Negative	***r = .81 (p = .004)***	*r = -.35 (p = .328)*	***r = -.90 (p = <.001)***
PANSS General	***r = .72 (p = .020)***	***r = -.84 (p = .002)***	*r* = -.32 (*p* = .365)
SANS	***r = .81 (p = .005)***	*r* = -.33 (*p* = .345)	***r = -.92 (p = <.001)***

Table 4.9 - Correlational Analysis: Neuropsychological Assessments/Clinical Measures: DISC1 t(1;11) Translocation Carriers (N=13)

- *p*-values were controlled for age, gender and current IQ (premorbid IQ where current IQ is the variable of interest). For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

4.7 Polygenic Risk Profile Scores: *DISC1 t*(1;11) Carriers by Sub-Group Diagnoses

Initial comparisons using one-way analysis of variance did not identify any significant differences between any of the polygenic risk profile scores (all p>.05) and any of the *t*(1;11) carrier diagnostic sub-groups, i.e. 'psychotic disorder', 'major depressive disorder' and/or 'other diagnoses'.

4.7.1 Polygenic Risk: Neuropsychology and Clinical Symptoms – *DISC1 t*(1;11) Carriers as a Group

As for all family, no significant associations were identified between any of the polygenic risk profile scores and any of the neuropsychological measures for *t*(1;11) carriers (all p>.05). There was, however, a significant association between *t*(1;11) carriers' polygenic risk for schizophrenia and the Positive and Negative Symptom Scale (PANSS) 'general symptoms' which remained significant after controlling for CNT (***r = .59, p = 0.035***) however this result became non-significant after correcting using the FDR procedure (tables 4.10 and 4.11).

	PANSS General Symptoms
	***r* (p_{FDR})**
Polygenic Risk for Schizophrenia	*r* = .59 **(*p* = .027)**

Table 4.10 – Correlational Analysis Results – Polygenic Risk for Schizophrenia – DISC1 t(1;11) Translocation Carriers (N=14)

Controlling for CNT	PANSS General Symptoms
	***r* (p_{FDR})**
Polygenic Risk for Schizophrenia	*r* = .59 (*p* = .035)

Table 4.11 – Correlational Analysis Results (Controlling for CNT) – Polygenic Risk for Schizophrenia – DISC1 t(1;11) Translocation Carriers (N=14)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

4.8 Self-Reported Measures of Personality and Mood: *DISC1 t*(1;11) Carriers

As the self-report questionnaire data was found to deviate from normality, non-parametric Kendall's tau-b correlational analyses were conducted with a specific focus on neuropsychological measures and clinical symptoms with *t*(1;11) carriers. No significant associations were found with any of the neuropsychological measures, however significant associations were identified between two sub-group measures from the Kings Schizotypy Questionnaire (KSQ), namely the KSQ 'Total Score' and 'Total Negative' scores (Table 4.12).

	Kings Schizotypy Questionnaire (KSQ)	
	'Total Score'	**'Total Negative'**
Clinical Measure	*'p' value/Kendall's tau-b correlation co-efficient* τ_b	
PANSS 'Positive Symptoms'	***p = .020,*** τ_b ***= .62***	***P = .020,*** τ_b ***= .64***

Table 4.12 – Correlational Analysis Results – Total Sub-Group Measures from the Kings Schizotypy Questionnaire (KSQ) and DISC1 t(1;11) Translocation Carriers (N=11)

Strong positive associations were found between positive symptomology in *t*(1;11) carriers and self-reported negative measures from the Kings Schizotypy Questionnaire. The KSQ 'Total Negative' sub-group comprises 'Social Isolation' and 'Social Anxiety'.

4.9 Discussion

4.9.1 Neuropsychological Measures

This is the first report of results from a full battery of neuropsychological assessments in individuals from the unique *t*(1;11) kindred. An obvious limitation is the unavoidably small sample sizes and possibility of Type II errors, but we have still been able to detect some effects of the *t*(1;11) balanced translocation on cognitive functions, especially reaction time, particularly in those individuals who have both the genetic risk factor (*DISC1 t*(1;11) balanced translocation) and psychotic disorder. Test results across all assessments reveal lower scores in all *t(*1;11) carriers, with the most severe seen in the group with psychotic disorders (schizophrenia, schizoaffective disorder and bipolar disorder). It is also evident that individuals with recurrent major depressive disorder scored lower than those with other (usually minor) diagnoses, mainly cyclothymia, and that the *t*(1;11) carriers scored lower than their non-translocation carrying relatives across all measures. Where results did not meet significance, possibly due to a lack of statistical power, effect sizes revealed moderate to large effects in a number of areas.

4.9.2 General Intelligence

From *t*(1;11) carriers sub-group analyses, current IQ was significantly impaired in those with psychotic disorder, and a particularly large difference between pre-morbid and current IQ scores was found between individuals with psychotic disorder and those with other diagnoses within the *DISC1* family. The mean pre-morbid IQ for *t(*1;11) carriers in this study (n=12) was 103.67 and 104.54 for non-carriers (n=15). These scores are in line with those previously obtained from an overlapping group of *t*(1;11) carriers in 2001 by Blackwood et al., (2001).

Reduced premorbid and current intelligence is commonly found in schizophrenia, but the particularly marked change from premorbid to current IQ within this kindred - especially in psychotic disorder – suggests that *DISC1* may increase the risk for major psychiatric disorder through a deterioration in general intelligence.

In those with both the translocation and psychotic disorder, the combination could produce a 'double hit' as the development of a psychotic illness would likely lead to a further negative impact on intelligence.

Two *t*(1;11) family members were receiving anti-psychotic medication (one of whom was also receiving anti-depressant medication); one *t*(1;11) carrier was receiving anti-depressant medication and one non-carrier was also receiving anti-depressant medication. Although antipsychotic medications have transformed the lives of those suffering from psychotic illness, they very often have negative effects and therefore come at a price. Antipsychotic medications target a key chemical brain transmitter – dopamine - which is also heavily involved with motor function (D Thomas & Dauner, 1992; Owens, D.C. 2014). The most common extrapyramidal symptoms produced as side-effects of antipsychotic medications include tardive dyskinesia, dystonic reactions, akinesia and Parkinsonism. As medication effects are known to have a deleterious effect on cognition, it is possible that this may have contributed to the marked change from premorbid to current IQ. No associations were found, however, between neuropsychological measures and chlorpromazine equivalent (CPZ) during analysis, therefore although medication effects are considered to have a negative impact on cognition, it does not appear to be a contributory factor within this kindred.

These results show that general intelligence (I.Q.) is impaired in *t*(1;11) family members with the translocation - especially those with a psychiatric diagnosis.

Although a high number of studies investigating *DISC1* and cognition have been conducted, few have specifically investigated general intelligence. Most of these studies obtained a measure of either premorbid or current I.Q. however unfortunately, these data were not comparable due to the variety of methodologies employed (see Chapter 2 for a full review). As discussed, Blackwood et al., (2001) reported premorbid I.Q. to be within the normal range in a number of individuals from the *t*(1;11) kindred, however it can now be seen from these results that there is a marked difference between premorbid and current I.Q. in carriers (especially those with psychosis).

DISC1 and general intelligence was also examined in two other studies and although no significant effects of *DISC1* genotype and cognition were revealed, Thomson et al., (2005) revealed a significant effect of *DISC1* genotype by sex interaction for older non-psychiatric females homozygous for the Cys allele of the *DISC1* SNP Ser704Cys (rs821616). This finding points to the possibility that variation in *DISC1* may affect normal cognitive development, especially in females.

More recently, Thomson and colleagues (2014) reported a nominal association between *DISC1* functional and putative regulatory variants and recurrent major depressive disorder and/or cognitive ability.

4.9.3 Attention and Processing Speed

It was also interesting to note that reaction time and, in particular, attention and processing speed were consistently found to be significantly reduced, as these results support the earlier auditory P300 ERP findings reported by Blackwood et al., (2001).

Further, these findings may also indicate the potential involvement of the *t*(1;11) balanced translocation in the development of structures within the temporal lobes which have previously been linked to abnormal P300 amplitude and latency in schizophrenia (McCarley, Nakamura et al. 2008).

These findings support previous neuropsychological studies examining *DISC1* and cognition, especially with regard to attention and processing speed. Visual attention has previously been reported to associate with a *DISC1* haplotype (HEP3) (Hennah et al., 2005) and Liu et al., (2006) reported an association between *DISC1* and impaired sustained attention.

In addition to the abnormal P300 findings reported by Blackwood et al., (2001), *DISC1* has also been associated with processing speed in several other studies including Burdick et al., (2005) in their study of schizophrenic patients. In this study, *DISC1* SNPs were associated with a rapid visual search task.

Visual reaction time was found to be associated with a rare 4-SNP *DISC1/TRAX* haplotype ('AATG') in work by Cannon et al., (2005) and Palo and colleagues examined category fluency in a large study of Finnish families and reported association between a common *DISC1* SNP, namely Ser704Cys (rs821616) and category fluency. This study also identified a further association with psychomotor processing speed and the *DISC1* SNP, rs980989. Recently, category fluency was examined using a novel computational linguistic approach and was found to be negatively associated with the *DISC1* SNP, rs12133766 (Nicodemus et al., 2014).

The ability to process information efficiently allows the successful execution of a range of other higher cognitive operations such as encoding and retrieval operations, decision processes, transformation of information held in active memory and perceptual processes, all of which rely on internal dynamics which are, to a certain extent, speed-dependent (Dickinson, Ramsey et al. 2007). Dickinson et al., (2007) also point out that neuropsychological studies have tended to overlook measures of processing speed in favour of trying to tease out potentially localisable cognitive impairments. Processing speed and other aspects of general intelligence are therefore promising performance dimensions worthy of further investigation in other genetic studies. For example, genetic variation in another gene - *CADM2* – was very recently found to associate with individual differences in information processing speed (Ibrahim-Verbaas et al., 2015).

4.9.4 Symptom Severity

It is perhaps surprising that there were no significant differences between translocation status and symptom severity rating scales, however a number of non-carriers are known to suffer from anxiety and/or depression which may have resulted in higher scores for negative/depressive symptoms. In this regard, a significant relationship was identified between translocation status for 'Anxiety' as measured by the Temperament Evaluation of the Memphis, Pisa, Paris and San Diego Auto Questionnaire (TEMPS-A) in which non-carriers reported greater anxiety than carriers, which may help to explain the non-significant clinical results.

Although non-carriers reported experiencing greater anxiety than carriers, a strong positive association was found with *t*(1;11) carriers between positive symptomology (as measured by the Positive and Negative Symptoms Scale) and the sub-group 'Total Negative' from the Kings Schizotypy Questionnaire (KSQ). The KSQ 'Total Negative' sub-group combines the self-reported measures of social anxiety and social isolation.

4.9.5 Symptom Severity and Neuropsychological Measures

In line with the main hypotheses, significant correlations were identified between symptom severity in the family (PANSS and SANS) and neuropsychological measures, particularly general intelligence (current IQ) and measures of attention and processing speed (simple and/or five-choice reaction time and motor speed).

Several studies have reported that negative symptoms are most commonly associated with cognitive functioning (Andreasen et al., 1990; Addington et al., 1991; Basso et al., 1998; Nieuwenstein et al., 2001; Lewandowski et al., 2011) and the results of this study support these findings with significant correlations between measures from both the PANSS and SANS with general intelligence (current IQ) and attention and processing speed. Executive function is most commonly associated with negative symptoms (Basso et al., 1998; Bozikas et al., 2004; Lewandowski et al., 2011;) which was not evident in this study, possibly due to the small sample size, however general intelligence has also been reported as being associated with negative symptoms (Basso et al., 1998; Berman et al., 1997; Addington et al., 1991) which concurs with the findings from this study. Cognitive impairment is a strong predictor of outcome in patients with major mental illness and neurocognitive dysfunction is highly associated with negative symptoms, making this a key treatment target.

4.9.6 Polygenic Risk Profile Scores

Contrary to the main hypotheses, polygenic risk for schizophrenia (PGRs) was not significantly different between family *t*(1;11) carriers and non-carriers although the risk profile scores for schizophrenia were higher in *t*(1;11) carriers. Polygenic risk for major depressive disorder (PGRmdd) was also non-significant but as with PGRs, the risk profile scores for depression were higher in *t*(1;11) carriers.

Polygenic risk for bipolar disorder (PGRbp), however, was significantly different between family *t*(1;11) carriers and non-carriers with higher risk scores seen in translocation carriers.

Recent studies have confirmed a molecular genetic overlap in schizophrenia, bipolar disorder and/or major depressive disorder (Purcell at al., 2009; Hamshere et al., 2011; Schulze et al., 2014). Looking at the results for the *t*(1;11) family, these may be better accounted for by creating a cross-disorder polygenic risk profile score to measure the joint effects of risk for schizophrenia, bipolar disorder and major depressive disorder. Similar studies have recently been conducted by Smoller et al (2013) and Whalley et al (2015) to investigate shared genetic aetiology and allow the examination of a broader set of common variants.

It would be likely that a cross-disorder polygenic risk approach would account for a greater proportion of overall risk than a polygenic risk score for a single psychiatric disorder (Whalley et al., 2015).

4.9.7 Polygenic Risk Profile Scores and Neuropsychological Measures

Again, contrary to the main hypotheses, polygenic risk for schizophrenia was not found to be significantly associated with neuropsychological measures, however, as this was of particular interest, it is worth noting that polygenic risk for schizophrenia marginally missed the significance threshold for association with simple reaction time in the family as a whole.

Recent studies have reported general intelligence as being highly polygenic (Davies et al., 2011) and poorer cognitive ability in old age, as well as greater cognitive decline between childhood and old age has been reported as being associated with an increased polygenic risk for schizophrenia (McIntosh et al., 2013).

The first molecular genetic test to confirm the genetic overlap between cognitive ability and risk for schizophrenia was conducted by Lencz et al., (2014) who reported that cognitive polygenic scores for schizophrenia cases were significantly lower than controls, and similarly, they reported an association between poorer general cognitive ability and polygenic risk for schizophrenia. Investigating polygenic risk profile scores and neurocognition is a promising area for future research as it could potentially shed light on the genetic risk of specific cognitive domains that may be impaired or unimpaired and help to establish risk for the later development of major mental illness.

4.9.8 Polygenic Risk Profile Scores and Symptom Severity

Again, contrary to the main hypotheses, polygenic risk for schizophrenia was not found to be significantly associated with symptom severity in the family. Initial findings suggested that PGRs was significantly associated with two sub-groups from the positive and negative symptoms scale (PANSS) namely 'total score' and 'general symptoms' however these results were not robust after correcting using the FDR procedure.

Investigating polygenic risk and symptom severity has the potential to provide important information that could be used clinically. Recent work by Ruderfer et al., (2014) reported the identification of a polygenic component that significantly distinguished between bipolar disorder and schizophrenia, thereby implicating a difference in the underlying genetic architecture of these disorders (Ruderfer et al., 2014).

Few studies could be found that specifically investigated polygenic risk and clinical symptoms which is a consideration for future work. Derks et al., (2012) reported significant associations between polygenic risk for schizophrenia and five psychosis dimensions (positive, negative, disorganised, manic and depressed) in their case-control sample.

The significant results were only found in the combined case-control group and not when the schizophrenia cases and controls were compared separately. Their study was unable to provide evidence of genetic risk for any specific symptom dimension of schizophrenia, however future collaborative work could help to elucidate the genetic risk of specific quantitative symptom dimensions by investigating the clinical symptom ratings of schizophrenia in combination with the clinical symptom ratings of bipolar disorder, major depressive disorder and unaffected controls (Derks et al., 2012).

4.9.9 Limitations

Firstly, investigating the *DISC1 t*(1;11) balanced translocation was limited by the unavoidably low numbers of affected individuals and their non-translocation carrying relatives. With this in mind, being able to recruit a total of 26 family members (carriers N=13, non-carriers N=13), each of whom completed all measures required for this work, enabled the identification of a large effect of the *t*(1;11) translocation.

Secondly, a further limitation is the investigation of a single family with a single-gene locus as although these studies provide important information about a particular group of psychoses and help to ascertain whether any such single-gene locus has a major effect on the risk of illness, it could well be the case that findings may only relate to that particular family and remain unique (Blackwood et al., 2001). In line with previous research by Blackwood et al., (2001) because of the rarity of the translocation it remains important to continue investigations with this family to identify any phenotypic differences between family members with and without the translocation, as well as between family members and unrelated individuals with major mental illnesses including schizophrenia, bipolar disorder and major depressive disorder which was the primary reason for recruiting a combined patients group.

A third limitation concerns medication status. From the *t*(1;11) carriers, two individuals were taking antipsychotic medication together with a mood stabiliser, one individual was receiving a mood stabiliser only, and one was receiving an antidepressant only. Chlorpromazine equivalent scores were established and association analyses were conducted to identify associations between medication status and any of the clinical or cognitive measures. The analyses proved to be non-significant and therefore CPZ scores were not included as covariates in the main analyses. This decision may have limited the results in view of the known extrapyramidal symptoms as side effects including Parkinsonism which could definitely have a negative impact on any measure that utilises fine motor function.

Fourth – it is acknowledged that a power calculation should have been performed, however this wasn't deemed appropriate due to the unique nature of the family and the fact that the aim was to recruit as many family members as possible. This will be discussed further in Chapter 6. Another statistical consideration is the presence of outliers which can be seen in a number of graphs. Outliers were not removed and are shown in the main graphs, however analyses were conducted with the main outlier removed in which the result remained significant. It should also be noted that there were a large number of analyses conducted as part of the main *a priori* hypotheses and also as a result of additional exploratory analyses due to the fact that the family are so rare and opportunities to conduct investigations are limited. To reduce the chance of Type II errors, all analyses were corrected using the FDR procedure, however it is noted that some studies prefer not to correct for multiple comparisons due to the fact that mathematical corrections can substantially increase the risk of accepting the null hypothesis (Rothman, K. J. 1990). These calculations reduce the statistical power which in turn can lead to problems interpreting the study results therefore in this study, both uncorrected and corrected results are shown.

A final limitation concerns the decision not to conduct direct statistical comparisons between the family groups (*t*(1;11) carriers and non-carriers) and the patient groups (schizophrenia and bipolar disorder) and/or unaffected control participants. Research by Glahn et al., (2007b) has suggested that family members' brains are anatomically very similar and that certain areas are highly heritable. Shared heredity within the family would significantly confound any direct comparisons between these family members and a group of unrelated individuals, which is the main reason the patient groups and unaffected control participants were recruited. By recruiting the patient and control groups we were able to conduct indirect comparisons on the effects of having a psychiatric illness in general to the effects of the *t*(1;11) translocation within the family without the need for direct statistical comparisons between the family and patients/control participants. In addition to the shared heredity, other confounding factors include age, geographical location, socio-economic status, education and employment.

4.9.10 Summary

In line with the main hypotheses, IQ was reduced in translocation carriers compared to non-carriers and although not significant, there was a moderate to large effect size. For translocation carriers, however, IQ was significantly reduced between diagnostic groups, as was premorbid to current IQ difference.

Measures of processing speed (reaction time and attention and processing speed) were also significantly reduced between translocation carriers and non-carriers.

Sample sizes in this study are small, and it is possible that analyses did not reach significance due to the unavoidable lack of power.

However as can be seen from Table 4.5, measures of effect size were calculated in an effort to identify whether any lack of significance might indeed be an effect of the *t*(1;11) balanced translocation which didn't reach significance purely due to the small numbers. Focussing on *t*(1;11) translocation carriers compared with non-carriers, moderate to large effect sizes were revealed in a number of cognitive domains including IQ, especially the reduction between premorbid to current IQ - suggesting the *t*(1;11) translocation has a developmental effect, negatively impacting on intelligence. Moderate to large effect sizes were also evident in measures of processing speed - particularly the symbol coding task which measures attention and processing speed, pointing to the potential involvement of the *t*(1;11) balanced translocation in the development of structures within the temporal lobes which have previously been linked to abnormal P300 amplitude and latency in schizophrenia.

Simple and five-choice reaction time tasks were also found to have large effect sizes, however it is possible that reaction time may be more impacted by current symptoms and medication as opposed to being directly attributable to an effect of the *t*(1;11) translocation. Although medication was not found to be significantly associated with any neuropsychological measures, it is possible that antipsychotic medication may have been a contributory factor in the significant associations identified between both measures of reaction time and symptom severity ratings by, for example, their known effects on fine motor function.

Contrary to hypotheses, polygenic risk for schizophrenia was not significantly different between translocation carriers and non-carriers, however it was significantly associated with symptom severity and marginally associated with neuropsychological measures. Polygenic risk for bipolar disorder was significantly different between translocation carriers and non-carriers and may better describe the phenotype of this kindred which does appear to have more cases of depression.

As previously mentioned, single family studies can be extremely helpful, especially when studying the psychoses. Although there is no doubt that the *DISC1 t*(1;11) kindred are truly unique - their rare genetic make-up providing the catalyst for over 40 years of progressive research into major psychiatric disorders - it remains a possibility that any findings could indeed be specifically related to their single lineage as opposed to potentially unravelling the common mechanisms in the universal population who develop major mental illness.

Notwithstanding, these results support the literature and suggest that variation in *DISC1* (especially the rare *t*(1;11) balanced translocation) affects neurodevelopmental processes, impacts upon neurocognitive function and increases risk for the later development of psychiatric illness.

Chapter 5: Results – Patients and Control Participants

5. Patients and Control Participants

5.1 Demographic Details

The primary aim of having a combined patients group was to provide a positive control group for the *DISC1* family in which there are mixed diagnoses.

Sample demographics for all patients and control subjects are shown in table 5.1.

Table 5.1 - Sample Demographics including Clinical Ratings – Patients and Control Participants

Sample Size (N=90)	**Patients (N=48)**	**Controls (N=42)**
Gender M/(F)	**34/(14)**	**24/(18)**
	Mean (SD)	***Mean (SD)***
Age	39.65 (11.65)	38.24 (14.40)
Premorbid IQ (NART)	110.42 (9.52)	111.29 (6.81)
Current IQ (WASI)	103.79 (17.21)	113.98 (12.01)
Premorbid to Current IQ Difference	-6.63 (11.52)	2.69 (9.83)
PANSS Total Score	52.52 (19.13)	31.45 (4.17)
PANSS Negative Symptoms	13.21 (7.26)	7.31 (1.40)
PANSS Positive Symptoms	11.92 (4.58)	7.14 (0.65)
PANSS General Symptoms	27.40 (9.52)	17.00 (3.51)
SANS	25.96 (22.04)	1.43 (5.02)
GAF	51.94 (17.49)	86.76 (8.07)
YMRS	2.27* (3.03)*	0.13† (0.81)†
HRSD	8.75* (7.99)*	0.78† (3.02)†
Anti-psychotic medication (CPZ Equivalent)**	475.14 (376.99)	0 (0)

*Table 5.1 – Sample demographics including Clinical Ratings for Patients and Control Participants. Positive and Negative Symptoms Scale (PANSS); Scale for the Assessment of Negative Symptoms (SANS); Global Assessment of Function (GAF); Young Mania Rating Scale (YMRS); Hamilton Rating Scale for Depression (HRSD), Chlorpromazine Equivalent (CPZ).*N=44 †N=38 **N=36*

5.1.1 Age, Gender, Premorbid IQ, Current IQ and IQ Difference

Patients (n=48) and controls (n=42) were compared using an independent samples *t*-test. No significant between-group differences were found for age (Figure 5.1), gender or premorbid IQ, however, as expected, current IQ was significantly reduced (t = -3.28, df = 83.9 $\boldsymbol{p = .002}$) (equal variances *not* assumed) in patients compared with control subjects, as was IQ difference (i.e. the difference between premorbid and current IQ) (equal variances assumed) (t = -4.10, df = 88, $\boldsymbol{p < .001}$) (Figure 5.2).

Mean Age for Combined Patients Group and Control Group

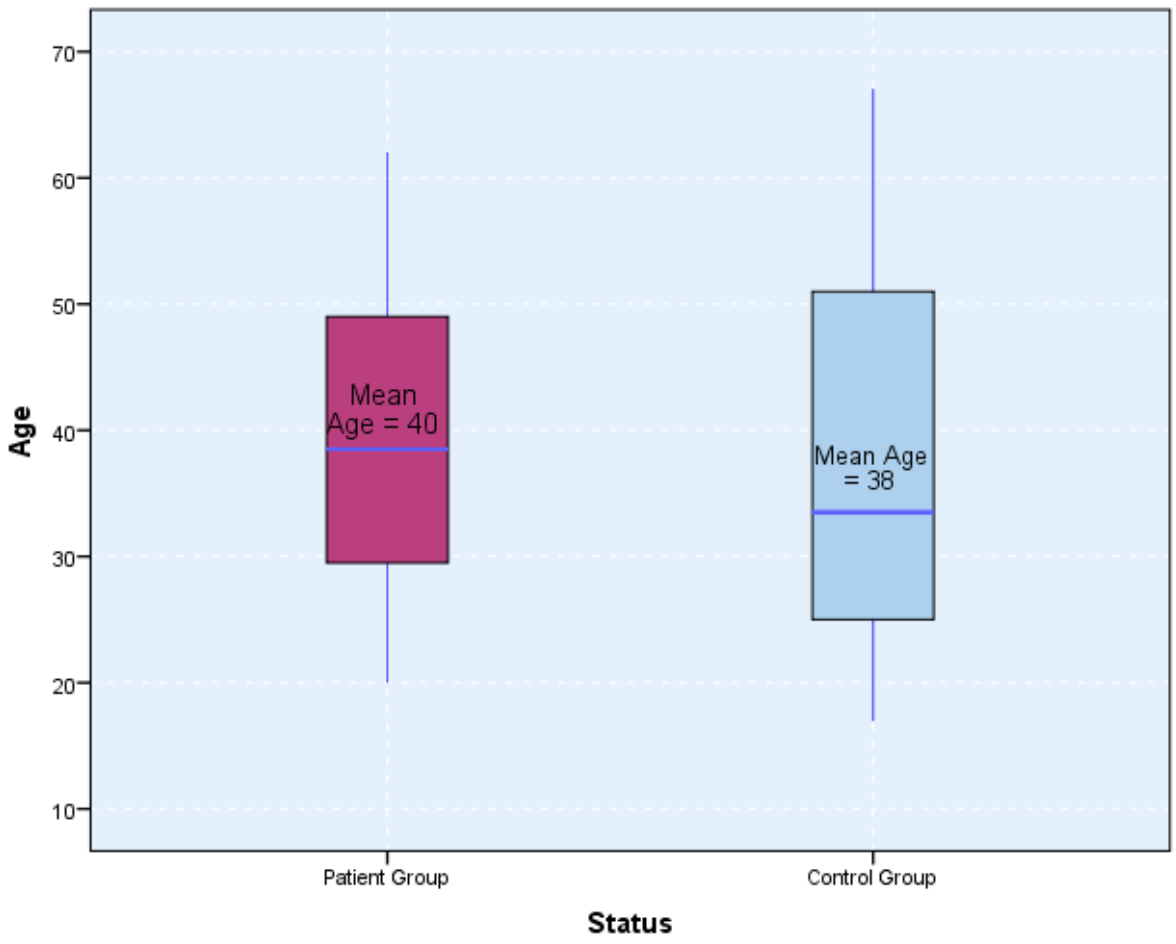


Figure 5.1 – Mean and Median Age for Patient and Control Groups

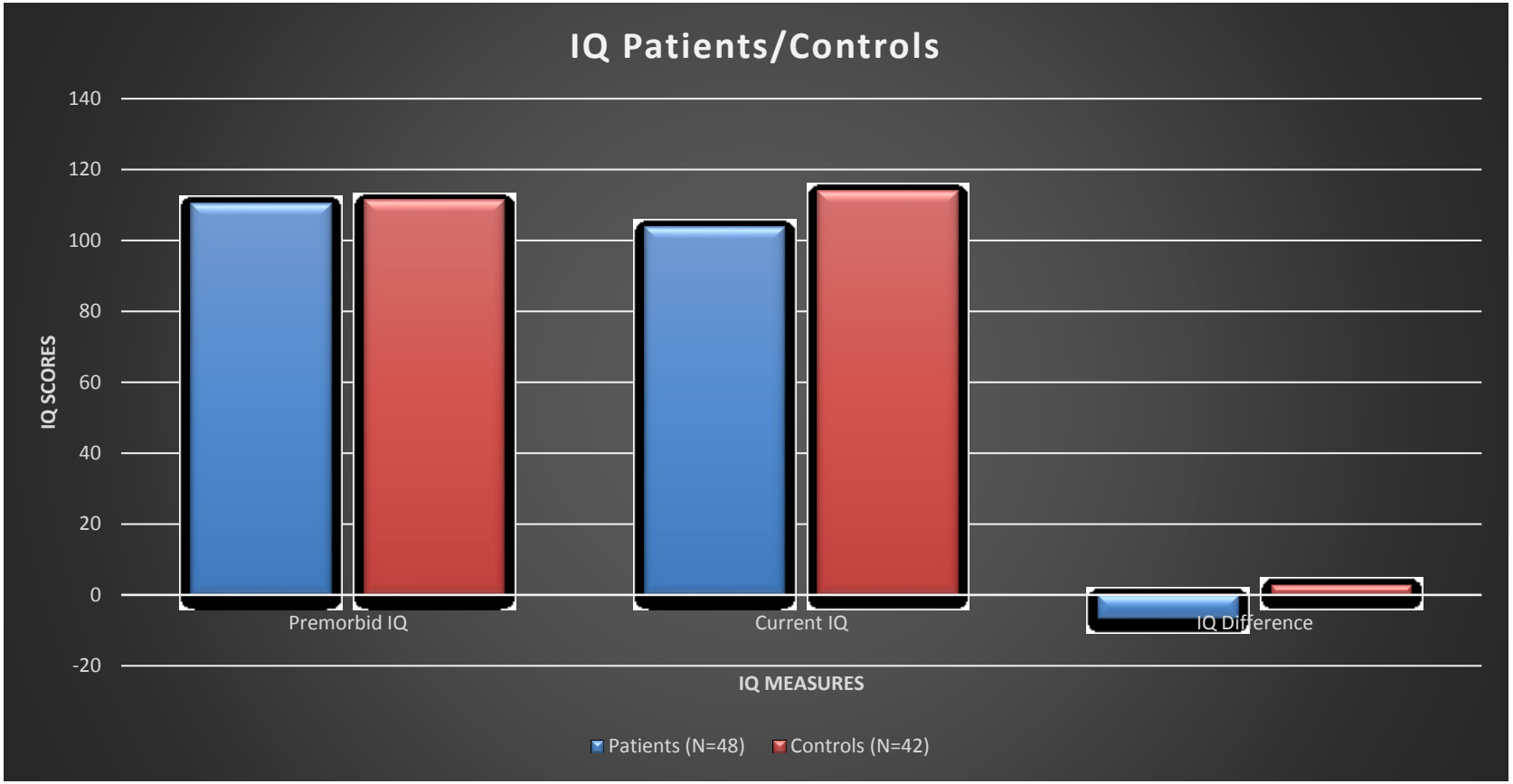


Figure 5.2 - Premorbid IQ, Current IQ and IQ Difference for all Patient and Control Samples.

5.1.2 Brief Assessment of Cognition in Schizophrenia (BACS)

Initial analysis using independent samples *t*-tests (equal variances *not* assumed for digit sequencing and motor speed tasks) revealed significantly reduced performances for patients compared to controls in all six BACS assessments (Figure 5.3). Controlling for age, gender and current IQ using a general linear model univariate analysis of covariance identified significantly poorer performances ($p<.05$) from the patient group for motor speed and attention and processing speed (using a symbol coding task).

Brief Assessment of Cognition in Schizophrenia: Patients and Controls

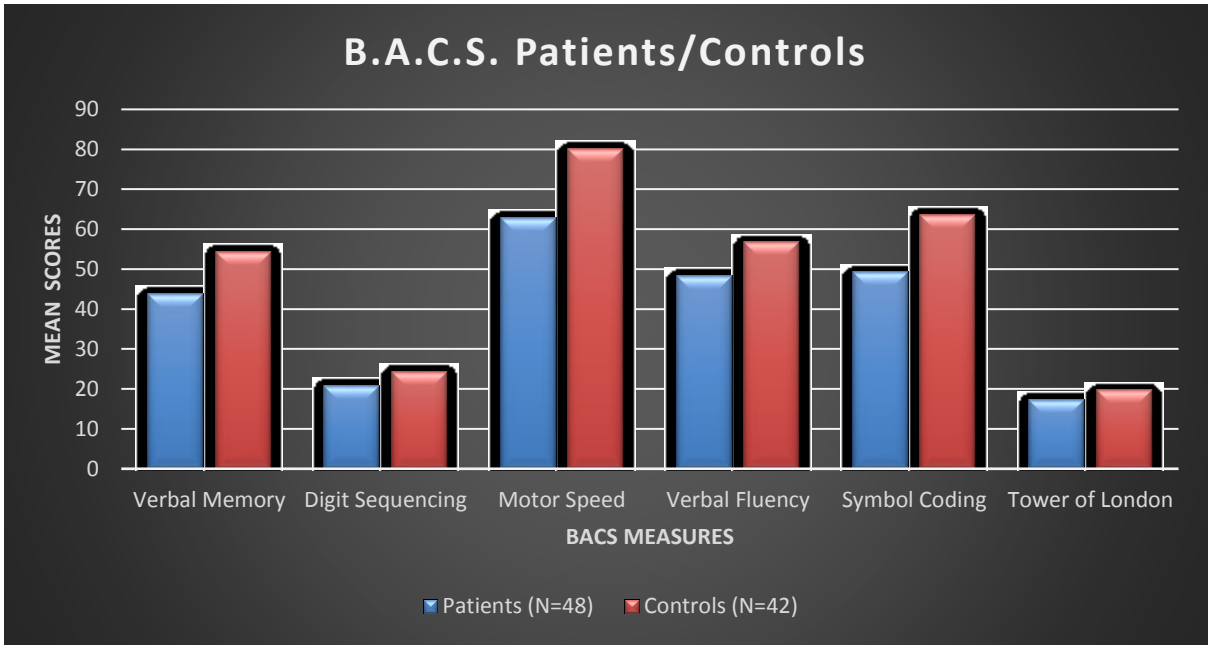


Figure 5.3 - Mean Raw Scores for Brief Assessment of Cognition in Schizophrenia (BACS): Patient and Control Groups

5.1.3 Cambridge Neuropsychological Test Automated Battery (CANTAB)

Initial comparisons using an independent samples *t*-test (equal variances *not* assumed) revealed significantly reduced performances ($p<.05$) from patients for both simple and five-choice reaction time tasks. Further comparisons using a general linear model univariate analysis of covariance (homogeneity of error variance met) remained significant for the five-choice reaction time task controlling for age, gender and current IQ ($F(1,81)$ 6.93, $\boldsymbol{p = 0.010}$). (Figure 5.4)

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Simple and Five-Choice Reaction Time Tasks: Patients and Controls

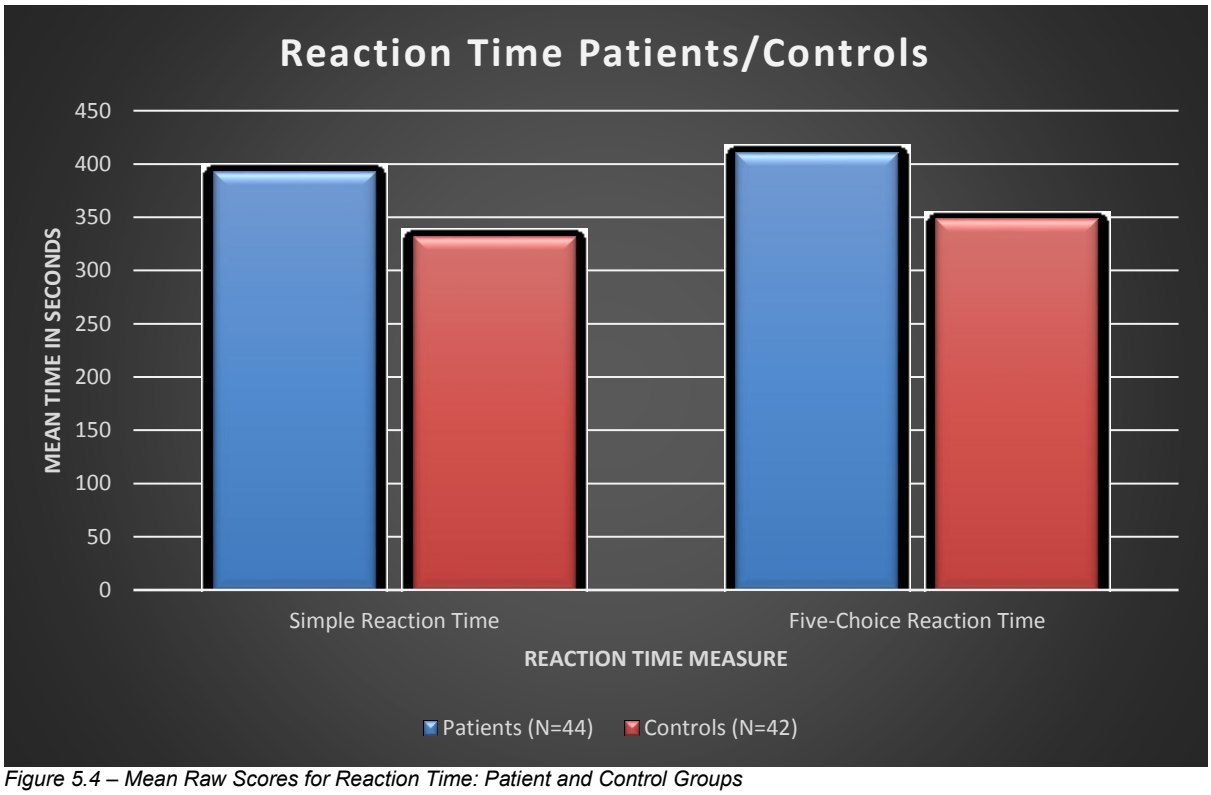


Figure 5.4 – Mean Raw Scores for Reaction Time: Patient and Control Groups

5.2 Clinical Symptom Rating Scales

Symptom severity was measured using a range of clinical rating scales including the Positive and Negative Symptoms Scale (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), the Global Assessment of Functioning (GAF), the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale for Depression (HRSD). Full details of these measures can be found in Chapter 3 (Methods).

5.2.1 Clinical Symptom Rating Scales: Patients and Controls

Direct comparisons of symptom severity were conducted between all patients (N=48) and control participants (N=42) using independent samples *t*-tests. As expected, all symptom severity ratings were significantly different between these groups ($p < .01$). As homogeneity of variance assumptions were violated, non-parametric Mann-Whitney U analysis were conducted which confirmed all significant results ($p < .01$).

5.3 Clinical Symptom Rating Scales and Neuropsychological Assessments

It was hypothesised that symptom severity, particularly positive and negative symptoms, would be significantly associated with measures of neuropsychology, in particular IQ and measures of processing speed. Clinical rating scales were therefore investigated to establish whether symptom severity associated with cognitive function in the combined patients group and also in patients by diagnosis.

5.3.1 Neuropsychological Assessments and Symptom Severity: Combined Patients Group

Pearson bivariate correlational analysis identified significant associations between measures of neuropsychology and symptom severity in patients.

Not all results were robust controlling for age, gender and current IQ (premorbid IQ where current IQ was the variable of interest). Current IQ was significantly associated with two measures from the positive and negative symptoms scale (PANSS), namely 'total score' and 'negative symptoms' and current IQ was also significantly associated with negative symptoms as measured by the SANS. These results were robust controlling for age, gender and current IQ. To reduce the possibility of Type II error, all significant *p*-values were corrected using the FDR procedure. Full details are provided in Table 5.2.

	Current IQ	Motor Speed
	***r* (p_{FDR})**	***r* (p_{FDR})**
PANSS Total	***r* = -.33, *p* = .029**	***r* = -.30, *p* = .041**
PANSS Positive	*r* = -.27, *p* = .076	***r* = -.32, *p* = .030**
PANSS Negative	***r* = -.39, *p* = .008**	***r* = -.36, *p* = .014**
SANS	***r* = -.47, *p* = .001**	***r*= -.31, *p* = .039**

Table 5.2 – Correlational Analysis: Neuropsychological Assessments/Clinical Measures - Patients Group (N=48)

p-values have been controlled for age, gender and current IQ (premorbid IQ where current IQ is the variable of interest). For all correlations, *p*-values were corrected using the FDR

5.4 Polygenic Risk Profile Scores: Patients and Control Participants

It was hypothesised that polygenic risk for schizophrenia would be significantly associated with the combined patients group and particularly patients with schizophrenia. It was also hypothesised that polygenic risk profile scores would be associated with measures of neuropsychology and symptom severity, in particular IQ, measures of processing speed and positive symptoms, especially in patients with schizophrenia.

5.4.1 Polygenic Risk Profile Scores: Patients and Control Participants

Initial analysis between the combined patients group (N=41) and control participants (N=34) using an independent samples *t*-test (equal variances assumed) reached significance for polygenic risk for schizophrenia (***p* = .050**) (Figure 5.5 and Tables 5.3 & 5.4). No significant differences were identified between patients and controls for polygenic risk for bipolar disorder or polygenic risk for major depressive disorder.

Polygenic Risk Score for Schizophrenia: Patients and Controls

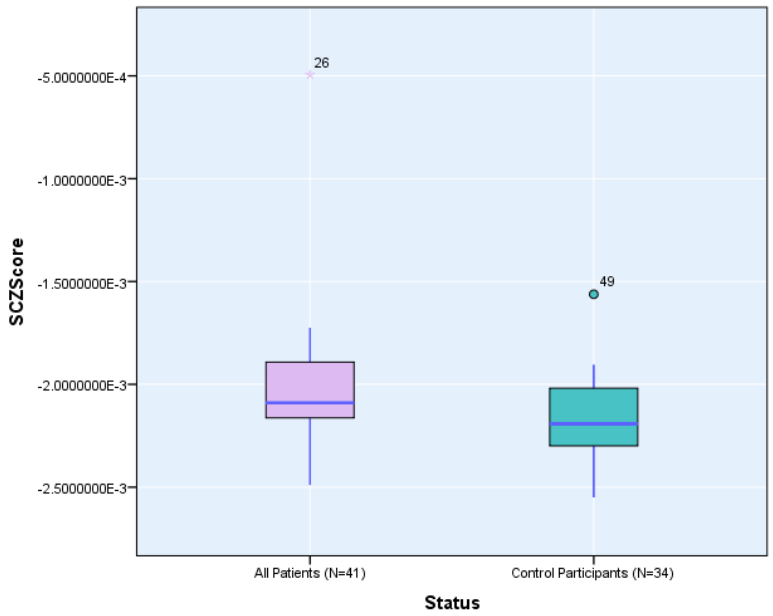


Figure 5.5 - Polygenic Risk for Schizophrenia: Combined Patients Group and Control Participants

Polygenic Risk Profile Score	N (All Patients)	Mean	Std. Deviation
Schizophrenia	41	-.002040856	.0003146393
Bipolar Disorder	41	.0012420535	.0005596922
Major Depressive Disorder	**41**	**.0083588015**	**.0007371641**

Table 5.3 - Polygenic Risk Profile Scores – Combined Patients Group (Schizophrenia & Bipolar Disorder Samples)

Polygenic Risk Profile Score	N	Mean	Std. Deviation
Schizophrenia	34	-.002166094	.0002067250
Bipolar Disorder	34	.0010939674	.0004490317
Major Depressive Disorder	**34**	**.0082641665**	**.0005667305**

Table 5.4 - Polygenic Risk Profile Scores – Control Participants

5.4.2 Polygenic Risk: Neuropsychological Assessments, Clinical Rating Scales and Self-Report Questionnaire Data – Combined Patients Group

Pearson bivariate correlational analysis identified a number of significant associations between polygenic risk for schizophrenia, bipolar disorder and/or major depressive disorder in the combined patients group (schizophrenia (N=25) and bipolar disorder (N=16)) with several neuropsychological and/or clinical measures.

(a) Polygenic Risk for Schizophrenia

From the neuropsychological test battery, polygenic risk for schizophrenia was significantly associated with IQ difference (***p = .048, r = -.31***) and marginally missed the significance threshold for current IQ. After controlling for CNT and correcting using the FDR procedure significance was lost (p = .051, r = -.31) (Tables 5.5 & 5.6). No significant associations were identified between polygenic risk for schizophrenia and any of the clinical measures or self-report questionnaires in the combined patients group.

	Current IQ	IQ Difference
	r ***(p_{FDR})***	***r*** ***(p_{FDR})***
Polygenic Risk for Schizophrenia	r = -.30, p = .052	r = -.31, p = .048

Table 5.5 – Correlational Analysis: Polygenic Risk for Schizophrenia - Combined Patients Group (N=41)

Controlling For CNT	Current IQ	IQ Difference
	r ***(p_{FDR})***	***r*** ***(p_{FDR})***
Polygenic Risk for Schizophrenia	r = -.30, p = .055	r = -.31, p = .051

Table 5.6 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Schizophrenia - Combined Patients Group (N=41)

For all correlations, p-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

(b) Polygenic Risk for Bipolar Disorder

In the combined patients group, polygenic risk for bipolar disorder was significantly associated with simple reaction time (***p = .033, r = .35***) and attention and processing speed (as assessed by a digit sequencing task) (***p = .041, r = -.32***), however these results became non-significant after controlling for CNT and correcting using the FDR procedure.

For clinical measures, polygenic risk for bipolar disorder was significantly associated with 'mania' as measured by the Young Mania Rating Scale (YMRS) (***p = .038, r = .34***) and remained significant after controlling for CNT, however this later became non-significant after correcting using the FDR procedure (Tables 5.7 & 5.8).

No significant associations were identified between polygenic risk for bipolar disorder and any self-report questionnaire data which is interesting as clinically rated mania but not self-rated mania was significantly associated with polygenic risk for bipolar disorder.

	Simple Reaction Time	Attention & Processing Speed	Young Mania Rating Scale
	$r\ (p_{FDR})$	$r\ (p_{FDR})$	$r\ (p_{FDR})$
Polygenic Risk for Bipolar Disorder	$r = .35, p = .033$	$r = -.32, p = .041$	$r = .34, p = .038$

Table 5.7 – Correlational Analysis: Polygenic Risk for Bipolar Disorder - Combined Patients Group (N=41)

Controlling For CNT	Simple Reaction Time	Attention & Processing Speed	Young Mania Rating Scale
	$r\ (p_{FDR})$	$r\ (p_{FDR})$	$r\ (p_{FDR})$
Polygenic Risk for Bipolar Disorder	$r = .31, p = .060$	$r = -.30, p = .060$	$r = .34, p = .045$

Table 5.8 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Bipolar Disorder - Combined Patients Group (N=41)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

(c) Polygenic Risk for Major Depressive Disorder

The majority of results were found with polygenic risk for major depressive disorder which included IQ difference (***p = .021, r = -.36***), motor speed (***p = .021, r = -.36***), verbal fluency (***p = .015, r = -.38***) and executive function (***p = .045, r = -.31***) (Table 5.9). All of these results remained significant after controlling for CNT and correcting using the FDR procedure (Table 5.10).

No significant associations were identified between polygenic risk for major depressive disorder and any of the clinical rating scales, however there was a significant association with the sub-group 'paranoid ideation' from the Kings Schizotypy Questionnaire (KSQ).

	IQ Difference	Motor Speed	Verbal Fluency	Executive Function	Paranoid Ideation
	r (p_{FDR})	*r (p_{FDR})*	*r (p_{FDR})*	*r (p_{FDR})*	*r (p_{FDR})*
Polygenic Risk for Major Depressive Disorder	***r = -.36 p = .021***	***r = -.36 p = .021***	***r = -.38 p = .015***	***r = -.31 p = .045***	***r = -.44 p = .023***

Table 5.9 – Correlational Analysis: Polygenic Risk for Major Depressive Disorder - Combined Patients Group (N=41)

Controlling For CNT	IQ Difference	Motor Speed	Verbal Fluency	Executive Function	Paranoid Ideation
	r (p_{FDR})	*r (p_{FDR})*	*r (p_{FDR})*	*r (p_{FDR})*	*r (p_{FDR})*
Polygenic Risk for Major Depressive Disorder	***r = -.37 p = .019***	***r = -.38 p = .017***	***r = -.37 p = .020***	***r = -.33 p = .035***	***r = -.48 p = .013***

Table 5.10 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Major Depressive Disorder - Combined Patients Group N=41)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

5.5 Sub-Group Comparisons: Schizophrenia and Bipolar Disorder

5.5.1 Age, Gender, Premorbid IQ, Current IQ & IQ Difference

Patients were sub-grouped according to diagnoses: schizophrenia (N=32), bipolar disorder (N=16). Sample demographics are provided in Table 5.11. Independent samples *t*-tests (equal variances assumed) did not identify any significant differences between patient groups for any of the demographic variables of age, gender, premorbid IQ, current IQ or IQ Difference (Figure 5.6).

Sample Demographics for Schizophrenia and Bipolar Disorder Samples

Sample Size (N=48)	**Schizophrenia (N=32)**	**Bipolar Disorder (N=16)**
Gender M/(F)	**23/(9)**	**11/(5)**
	Mean (SD)	***Mean (SD)***
Age	37.84 (9.97)	43.25 (14.12)
Premorbid IQ (NART)	109.53 (10.28)	112.19 (7.80)
Current IQ (WASI)	103.16 (16.70)	105.06 (18.88)
Premorbid to Current IQ Difference	-6.38 (9.71)	-7.13 (14.84)
PANSS Total Score	55.19 (20.53)	47.19 (15.14)
PANSS Negative Symptoms	14.41 (7.80)	10.81 (5.50)
PANSS Positive Symptoms	12.69 (4.89)	10.38 (3.52)
PANSS General Symptoms	28.09 (9.84)	26.00 (9.00)
SANS	28.88 (22.65)	20.13 (20.17)
GAF	48.09 (17.31)	59.63 (15.65)
YMRS	1.54* (1.91)*	3.56 (4.11)
HRSD	9.18* (8.43)*	8.00 (7.38)
Anti-psychotic medication (CPZ Equivalent)**	515.52 (397.88)	307.86 (223.08)

*Table 5.11 – Sample Demographics including Clinical Ratings for Schizophrenia and Bipolar Disorder Samples. Positive and Negative Symptoms Scale (PANSS); Scale for the Assessment of Negative Symptoms (SANS); Global Assessment of Function (GAF); Young Mania Rating Scale (YMRS); Hamilton Rating Scale for Depression (HRSD), Chlorpromazine Equivalent (CPZ).*N=28 **N=29 (Scz) N=7 (BP)*

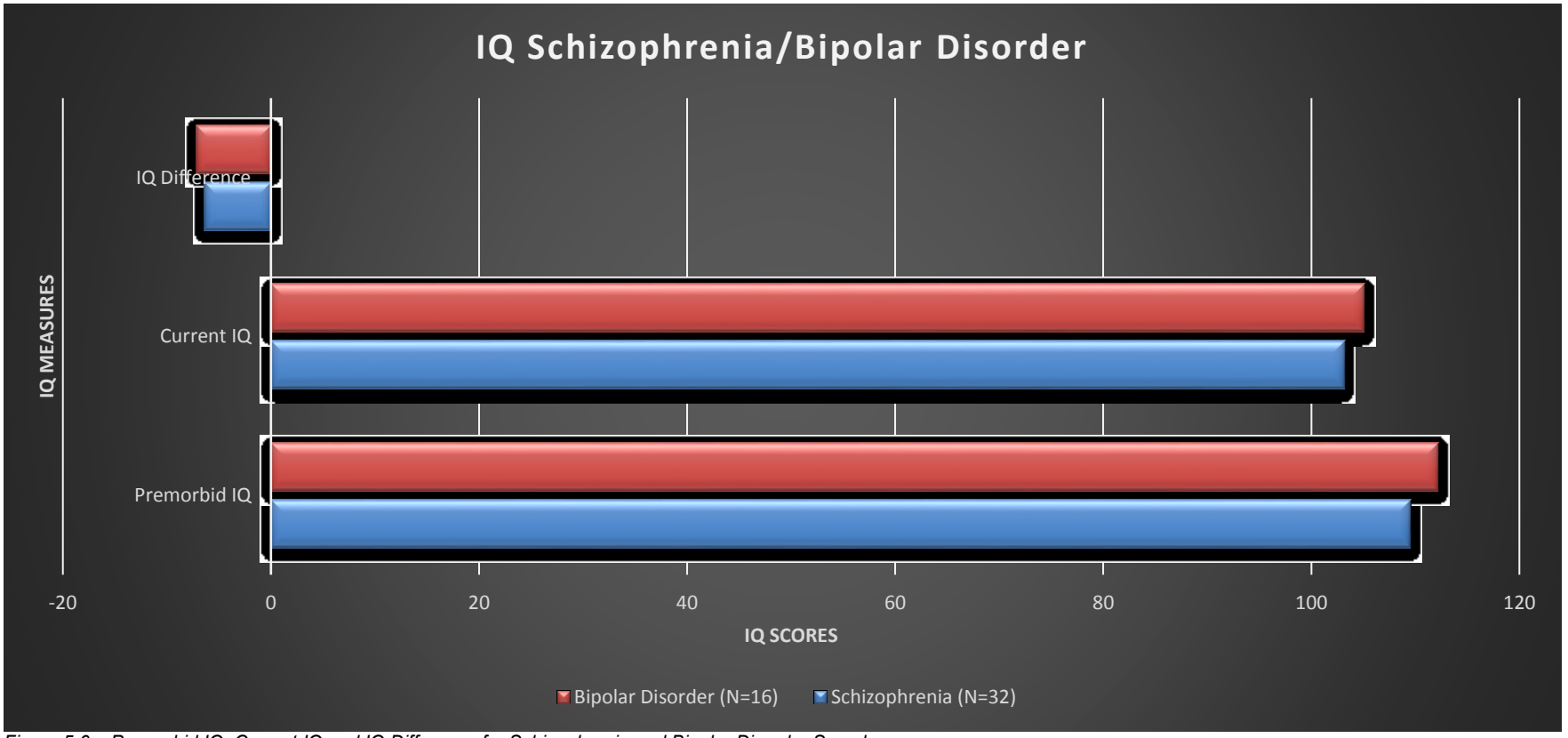


Figure 5.6 – Premorbid IQ, Current IQ and IQ Difference for Schizophrenia and Bipolar Disorder Samples

5.5.2 Brief Assessment of Cognition in Schizophrenia (BACS): Schizophrenia and Bipolar Disorder

Initial analyses using independent samples *t*-tests (equal variances assumed) did not identify any significant between-group differences for any of the six BACS assessments (see Table 5.12 for raw score means and standard deviations).

Controlling for age, gender and current IQ using a general linear model univariate analysis of covariance (homogeneity of error variance met) identified significantly poorer performances ($p<.05$) from patients with schizophrenia for verbal memory (as assessed by a list-learning task) ($F(1,43)$ 4.98, ***p*=.031**) and motor speed (as assessed by a token motor task) ($F(1,43)$ 5.14, ***p*=.028**). Attention and processing speed (as assessed by a symbol coding task) marginally failed to reach the significance threshold ($p=.052$) (Figures 5.7 and 5.8).

These results could, conceivably, be attributable to antipsychotic medication effects as 29 of 32 patients with schizophrenia and 7 of 16 patients with bipolar disorder were receiving antipsychotic medication. This is particularly relevant when considering the motor speed task and the powerful effects antipsychotics can exert on fine motor function. An independent samples *t*-tests (equality of variances met), did not identify any significant differences in antipsychotic medication (CPZ Equivalent) between patient groups and further correlational analyses did not identify any significant associations between antipsychotic medication and any of the BACS assessments. As a result of these findings, CPZ equivalents were not controlled for in the main analyses, however this omission may have limited these results and is a factor that should be addressed in future work.

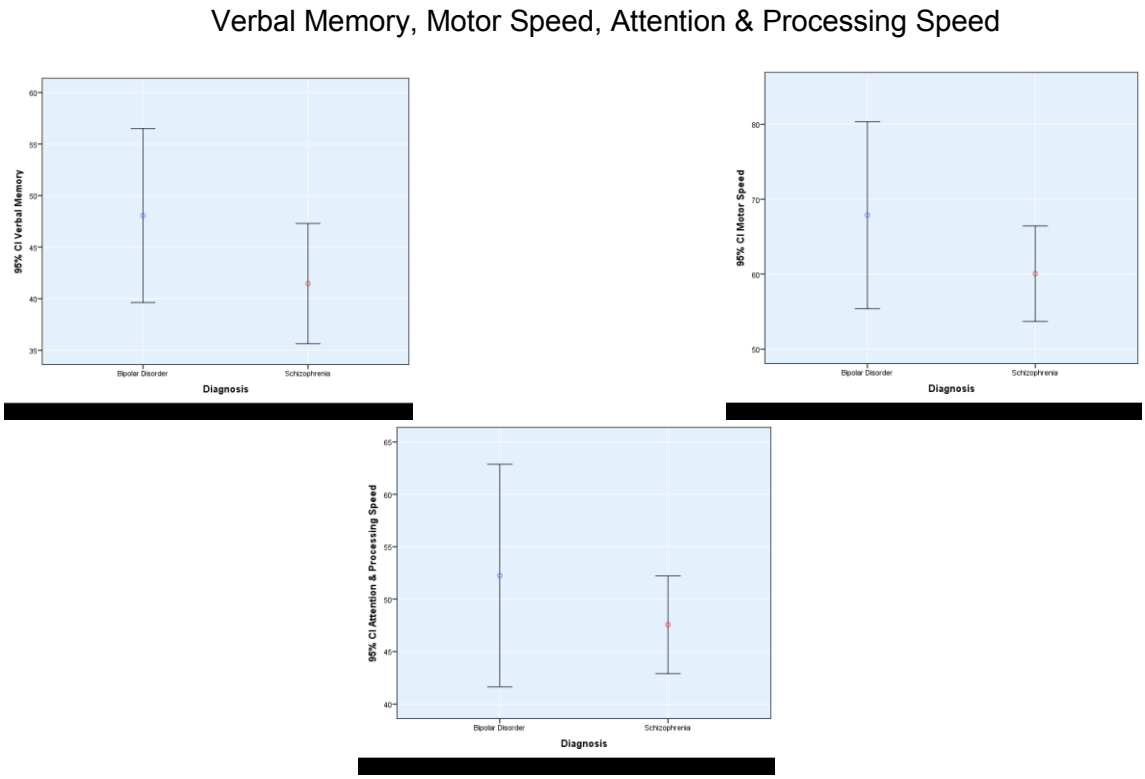


*Figure 5.7 - Error Bar Graphs for Verbal Memory (**p = .031**), Motor Speed (**p = .028**) and Attention & Processing Speed (p = .052) for Schizophrenia and Bipolar Disorder Samples*

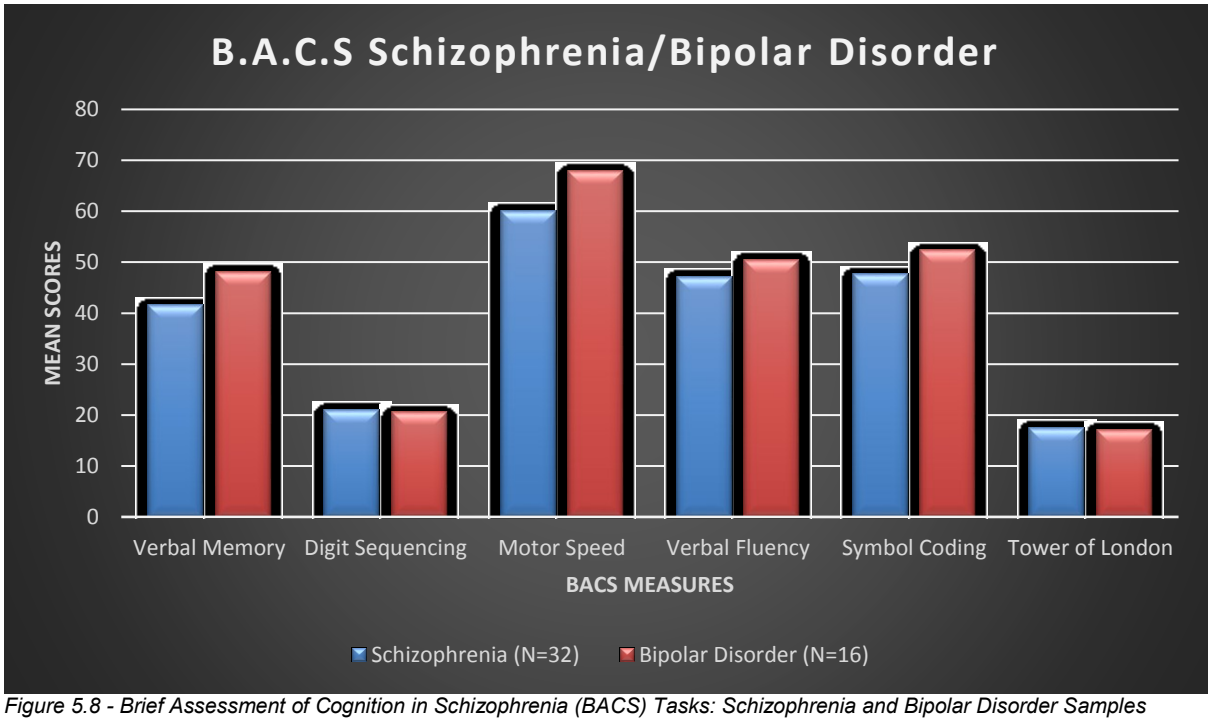


Figure 5.8 - Brief Assessment of Cognition in Schizophrenia (BACS) Tasks: Schizophrenia and Bipolar Disorder Samples

Sample Raw Scores for BACS and CANTAB

(Brief Assessment of Cognition in Schizophrenia and Cambridge Neuropsychological Test Automated Battery)

COGNITIVE DOMAIN/ BACS/CANTAB TASK	**SCHIZOPHRENIA RAW SCORES (N=32)**	**BIPOLAR DISORDER RAW SCORES (N=16)**
	Mean (Standard Deviation)	Mean (Standard Deviation)
VERBAL MEMORY: (LIST LEARNING TASK)	41.47 (16.20)	48.06 (15.85)
WORKING MEMORY: (DIGIT SEQUENCING TASK)	20.94 (5.28)	20.44 (7.52)
MOTOR SPEED: (TOKEN MOTOR TASK)	60.06 (17.70)	67.88 (23.44)
PROCESSING SPEED: (VERBAL FLUENCY TASK)	47.13 (14.11)	50.44 (17.54)
ATTENTION & PROCESSING SPEED: (SYMBOL CODING TASK)	47.56 (12.93)	52.25 (19.92)
EXECUTIVE FUNCTION: (TOWER OF LONDON TASK)	17.38 (3.88)	17.06 (5.71)
SIMPLE REACTION TIME (CANTAB)	367.50 (108.68)	435.58 (217.73)
FIVE-CHOICE REACTION TIME (CANTAB)	399.84 (100.38)	427.85 (175.70)

Table 5.12 – Brief Assessment of Cognition in Schizophrenia (BACS) and Cambridge Neuropsychological Test Automated Battery (CANTAB) Raw Score Means and Standard Deviations for Schizophrenia (N=32) and Bipolar Disorder (N=16) Samples

5.5.3 Cambridge Neuropsychological Test Automated Battery (CANTAB): Schizophrenia and Bipolar Disorder Samples

No significant differences were identified between the schizophrenia and bipolar disorder samples for either simple or five-choice reaction time tasks (see Table 5.12 for raw score means and standard deviations).

5.6 Clinical Symptom Rating Scales

Symptom severity was measured using a range of clinical rating scales including the Positive and Negative Symptoms Scale (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), the Global Assessment of Functioning (GAF), the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale for Depression (HRSD). Full details of these measures can be found in Chapter 3 (Methods).

5.6.1 Clinical Symptom Rating Scales: Patients by Diagnosis

Direct comparisons of symptom severity were conducted between the schizophrenia and bipolar disorder samples using independent samples *t*-tests which identified a significant difference in overall functioning as assessed by the Global Assessment of Function (***p<.05***). As homogeneity of variance assumptions were violated, a non-parametric Mann-Whitney U test was conducted which confirmed significance (***U=149.5, p = .020***). All other clinical rating scales proved to be non-significant.

5.7 Clinical Symptom Rating Scales and Neuropsychological Assessments

It was hypothesised that symptom severity, particularly positive and negative symptoms, would be significantly associated with measures of neuropsychology, in particular IQ and measures of processing speed. Clinical symptom rating scales were therefore investigated to establish whether symptom severity associated with cognitive function in patients by diagnosis.

5.7.1 Neuropsychological Assessments and Symptom Severity: Schizophrenia

Current IQ in the schizophrenia sample was significantly associated with negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) (***r = -.41, p = .028***) and was robust controlling for age, gender and premorbid IQ.

5.7.2 Neuropsychological Assessments and Symptom Severity: Bipolar Disorder

Current IQ in the bipolar disorder sample was also significantly associated with 'negative symptoms' as measured by both the Positive and Negative Symptoms Scale (PANSS) (***r = -.71, p = .007***) and the Scale for the Assessment of Negative Symptoms (SANS) (***r = -.61, p = .025***). Both results were robust controlling for age, gender and premorbid IQ.

Stronger correlations in bipolar disorder are unusual and analysis of polygenic risk profile scores may offer a more neurodevelopmental basis for these unexpected results which appear to point to the effects of bipolar disorder regardless of whether diagnoses are combined or separated.

5.8 Polygenic Risk Profile Scores: Schizophrenia and Bipolar Disorder Samples

A significant difference (***t(39) -3.33***, ***p = .002***) was identified using independent samples *t*-tests (equal variances assumed) between these patient groups for polygenic risk for bipolar disorder (Figure 5.10 and Tables 5.13 & 5.14). There were no significant differences between patient groups with polygenic risk for schizophrenia or major depressive disorder.

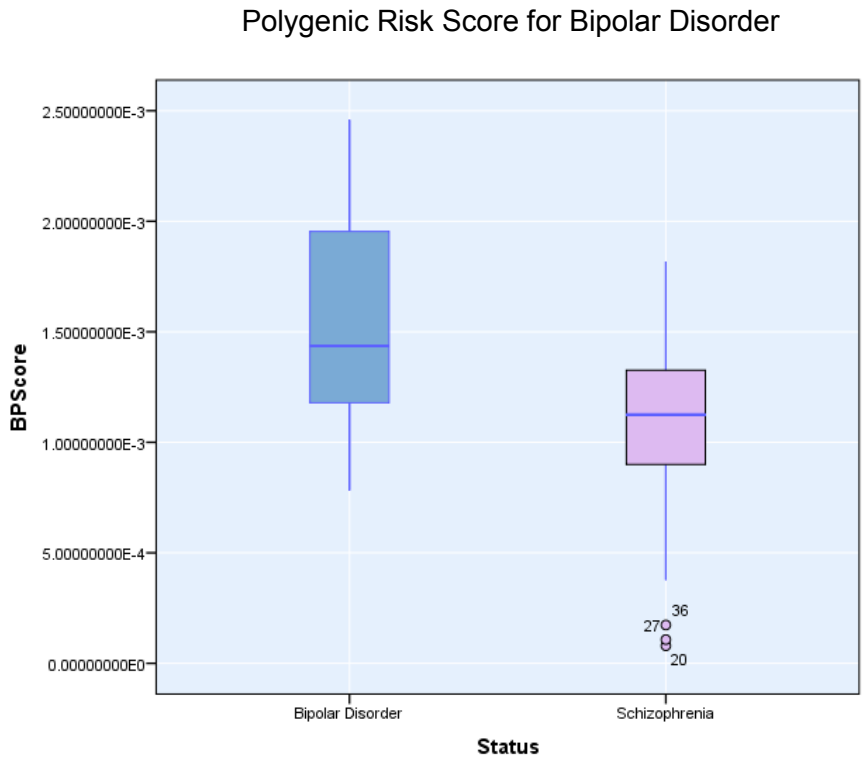


Figure 5.10 - Polygenic Risk for Bipolar Disorder: Schizophrenia (N=25) and Bipolar Disorder (N=16) Samples

Polygenic Risk Profile Score	N	Mean	Std. Deviation
Schizophrenia	25	-.002027400	.0003757594
Bipolar Disorder	25	.001034114	.0004951135
Major Depressive Disorder	**25**	**.008339230**	**.0008024925**

Table 5.13 - Polygenic Risk Profile Scores: Schizophrenia Participants

Table 5.14 – Polygenic Risk Profile Scores: Bipolar Disorder Participants

Polygenic Risk Profile Score	N	Mean	Std. Deviation
Schizophrenia	16	-.002061881	.0001931551
Bipolar Disorder	16	.001566959	.0005083912
Major Depressive Disorder	**16**	**.008389383**	**.0006458089**

5.8.1 Polygenic Risk Profile Scores: Schizophrenia, Bipolar Disorder and Control Participants

Finally, comparisons using a one-way analysis of variance were conducted between patients with schizophrenia, patients with bipolar disorder and control participants which identified a significant between-groups difference (***F(2,72) 6.969, p = .002***). Post hoc tests revealed significant differences between polygenic risk for bipolar disorder in patients with bipolar disorder and both patients with schizophrenia (***p = .003***) and control participants (***p = .005***) (Figure 5.11 and Tables 5.4, 5.13 & 5.14).

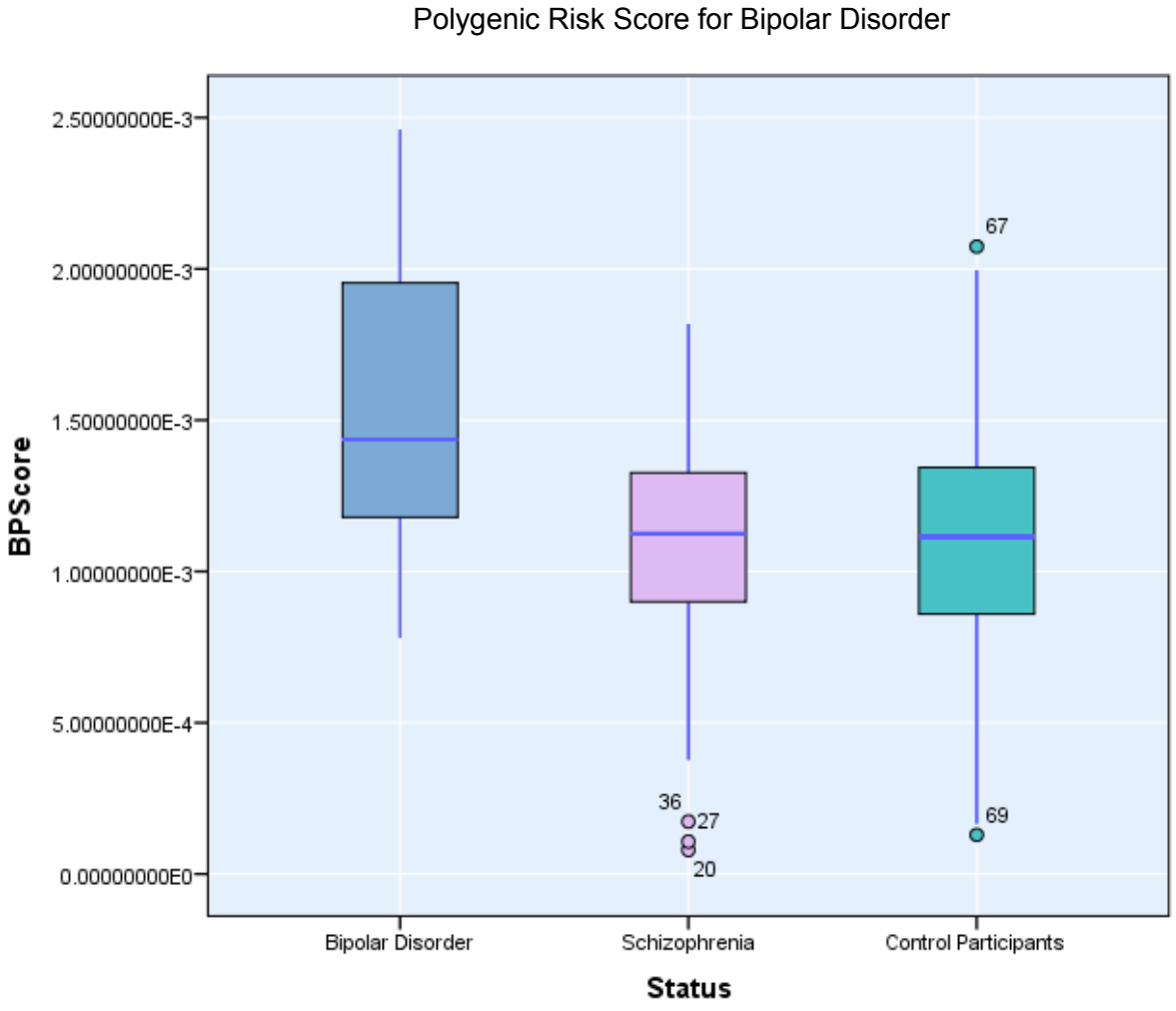


Figure 5.11 - Polygenic Risk for Bipolar Disorder: Schizophrenia Sample (N=25), Bipolar Disorder Sample (N=16) and Control Participants (N=34)

5.8.2 Polygenic Risk: Neuropsychological Assessments, Clinical Rating Scales and Self-Report Questionnaire Data – Schizophrenia Patients

Patients were split by diagnosis and their polygenic risk profile scores for each of schizophrenia, bipolar disorder and major depressive disorder were compared with neuropsychological, clinical and self-report measures.

(a) Schizophrenia Patient Group: Polygenic Risk for Schizophrenia

No significant results were identified for any of the neuropsychological or clinical measures in patients with schizophrenia.

(b) Schizophrenia Patient Group: Polygenic Risk for Bipolar Disorder

As with previous results, no significant associations were identified for any neuropsychological assessment, clinical measure and/or self-report questionnaire data.

(c) Schizophrenia Patient Group: Polygenic Risk for Major Depressive Disorder

Again, there were no significant associations in the schizophrenic sample between any of the neuropsychological; clinical or self-report questionnaires and polygenic risk for major depressive disorder.

5.8.3 Polygenic Risk: Neuropsychological Assessments, Clinical Rating Scales and Self-Report Questionnaire Data – Bipolar Disorder Patients

There were a number of significant associations identified in the bipolar disorder sample for each of the polygenic risk profile scores and/or neuropsychological, clinical and self-report measures, the majority of which remained significant after controlling for CNT.

(a) Bipolar Disorder Patients: Polygenic Risk for Schizophrenia

For neuropsychological assessments, current IQ and premorbid to current IQ difference were found to be significantly associated with polygenic risk for schizophrenia in patients with bipolar disorder (***r* = -.52, *p* = .039*** and ***r* = -.62, *p* = .011*** respectively). After controlling for CNT, premorbid to current IQ difference remained significant (***r* = -.58, *p* = .023***).

No significant associations were identified between polygenic risk for schizophrenia and any of the clinical measures in the bipolar disorder sample. Self-report questionnaire data revealed a significant association between polygenic risk for schizophrenia and the sub-group measure 'irritable' from the Temperament Evaluation of the Memphis, Pisa, Paris and San-Diego Auto-Questionnaire (TEMPS-A) (***r* = -.62, *p* = .031***), however this result became non-significant after controlling for CNT.

All results became non-significant after correcting using the FDR procedure.

(b) Bipolar Disorder Patients: Polygenic Risk for Bipolar Disorder

For neuropsychological assessments, current IQ and premorbid to current IQ difference were significantly associated with polygenic risk for bipolar disorder (***r = -.59, p = .016*** and ***r = -.54, p = .031*** respectively). After controlling for CNT, current IQ remained significant (***r = -.61, p = .015*** and $r = -.51$, $p = .053$ respectively).

Premorbid IQ was significantly associated with polygenic risk for bipolar disorder after controlling for CNT (***r = -.61, p = .005***) but not before ($r = -.39$, $p = .128$). All results remained significant after correcting using the FDR procedure. There were no significant associations between polygenic risk for bipolar disorder and any clinical or self-report measures.

(c) Bipolar Disorder Patients: Polygenic Risk for Major Depressive Disorder

From the neuropsychological test battery, IQ, premorbid to current IQ difference, five-choice reaction time and motor speed were all found to be significantly associated with polygenic risk for major depressive disorder. For symptom severity in the bipolar sample, negative symptoms as measured by the Positive and Negative Symptoms Sale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) were also significantly associated with polygenic risk for major depressive disorder and remained significant after controlling for CNT and correcting using the FDR procedure (Tables 5.15 & 5.16). There were no significant associations between polygenic risk for major depressive disorder and any self-report questionnaire data.

	Current IQ	IQ Difference	Five-Choice Reaction Time	Motor Speed	PANSS Negative	SANS Negative
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
Polygenic Risk for Major Depressive Disorder	***r* = -.55** ***p* = .028**	***r* = -.65** ***p* = .006**	***r* = .54** ***p* = .030**	***r* = -.63** ***p* = .009**	***r* = .59** ***p* = .016**	***r* = .55** ***p* = .028**

Table 5.15 – Correlational Analysis: Polygenic Risk for Major Depressive Disorder - Bipolar Disorder Sample (N=16)

Controlling For CNT	Current IQ	IQ Difference	Five-Choice Reaction Time	Motor Speed	PANSS Negative	SANS Negative
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
Polygenic Risk for Major Depressive Disorder	***r* = -.54** ***p* = .040**	***r* = -.67** ***p* = .006**	*r* = .47 *p* = .074	***r* = -.62** ***p* = .015**	***r* = .66** ***p* = .007**	***r* = .59** ***p* = .019**

Table 5.16 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Major Depressive Disorder - Bipolar Disorder Sample (N=16)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

In additional exploratory analysis, neuropsychological measures of verbal memory, verbal fluency and executive function were found to be significantly associated with polygenic risk for major depressive disorder, as was the total score from the PANSS and a measure of overall function as assessed by the Global Assessment of Function (GAF). The majority of these results remained significant after controlling for CNT and correcting using the FDR procedure (Tables 5.17 & 5.18).

	Verbal Memory	Verbal Fluency	Executive Function	PANSS Total	Function (GAF)
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
Polygenic Risk for Major Depressive Disorder	***r* = -.57** ***p* = .020**	***r* = -.60** ***p* = .014**	***r* = -.55** ***p* = .028**	***r* = .54** ***p* = .032**	***r* = -.61** ***p* = .012**

Table 5.17 – Correlational Analysis: Polygenic Risk for Major Depressive Disorder - Bipolar Disorder Sample (N=16)

Controlling for CNT	Verbal Memory	Verbal Fluency	Executive Function	PANSS Total	Function (GAF)
	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**	***r* (p_{FDR})**
Polygenic Risk for Major Depressive Disorder	*r* = -.52 *p* = .049	***r* = -.62** ***p* = .014**	*r* = -.51 *p* = .053	***r* = .55** ***p* = .035**	***r* = -.67** ***p* = .006**

Table 5.18 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Major Depressive Disorder - Bipolar Disorder Sample (N=16)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

5.8.4 Polygenic Risk: Neuropsychological Assessments, Clinical Rating Scales and Self-Report Questionnaire Data – Control Participants

Polygenic risk profile scores for control participants were also compared with neuropsychological assessments, clinical measures and self-report questionnaires.

(a) Polygenic Risk for Schizophrenia: Control Participants

There were no significant associations between polygenic risk for schizophrenia with neuropsychological measures or clinical ratings. Significant associations were identified, however with the self-reported questionnaire data in which two sub-group measures from the Kings Schizotypy Questionnaire (KSQ), namely 'Recurrent Illusions 1' and 'Magical Thinking' were both significantly associated with polygenic risk for schizophrenia. These results remained significant after controlling for CNT and correcting using the FDR procedure (Tables 5.19 & 5.20).

	Recurrent Illusions 1 (KSQ)	Magical Thinking (KSQ)
	$r\ (p_{FDR})$	$r\ (p_{FDR})$
Polygenic Risk for Schizophrenia	***r = .45, p = .012***	***r = .40, p = .027***

Table 5.19 – Correlational Analysis: Polygenic Risk for Schizophrenia - Control Participants (N=34)

Controlling For CNT	Recurrent Illusions 1 (KSQ)	Magical Thinking (KSQ)
	$r\ (p_{FDR})$	$r\ (p_{FDR})$
Polygenic Risk for Schizophrenia	***r = .47, p = .010***	***r = .42, p = .025***

Table 5.20 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Schizophrenia - Control Participants (N=34)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

(b) Polygenic Risk for Bipolar Disorder: Control Participants

No significant associations were identified for any of the neuropsychological or clinical measures in this sample, however, as with previous results, a significant association was identified between polygenic risk for bipolar disorder and the 'Recurrent Illusions 1' sub-group from the Kings Schizotypy Questionnaire (KSQ) which remained significant after controlling for CNT and correcting using the FDR procedure (Tables 5.21 & 5.22).

	Recurrent Illusions 1 (KSQ)
	***r* (p_{FDR})**
Polygenic Risk for Bipolar Disorder	***r* = .51, *p* = .004**

Table 5.21 – Correlational Analysis: Polygenic Risk for Bipolar Disorder - Control Participants (N=34)

Controlling For CNT	**Recurrent Illusions 1 (KSQ)**
	***r* (p_{FDR})**
Polygenic Risk for Bipolar Disorder	***r* = .51, *p* = .004**

Table 5.22 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Bipolar Disorder - Control Participants (N=34)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

(c) Polygenic Risk for Major Depressive Disorder: Control Participants

From the neuropsychological test battery, attention and processing speed (as assessed by a digit sequencing task) was significantly associated with polygenic risk for major depressive disorder (***r = -.45, p = .007***) and remained significant after controlling for CNT and correcting using the FDR procedure (Tables 5.23 and 5.24).

No significant associations were identified for any of the clinical rating scales in this sample, however, as with previous results, the sub-group 'Recurrent Illusions 1' from the Kings Schizotypy Questionnaire (KSQ) was significantly associated with polygenic risk for major depressive disorder and was robust controlling for CNT and correcting using the FDR procedure (Tables 5.23 and 5.24).

	Attention & Processing Speed	Recurrent Illusions 1 (KSQ)
	r ***(p_{FDR})***	***r*** ***(p_{FDR})***
Polygenic Risk for Major Depressive Disorder	***r = -.45, p = .007***	***r = -.43, p = .017***

Table 5.23 – Correlational Analysis: Polygenic Risk for Major Depressive Disorder - Control Participants (N=34)

Controlling For CNT	**Attention & Processing Speed**	**Recurrent Illusions 1 (KSQ)**
	r ***(p_{FDR})***	***r*** ***(p_{FDR})***
Polygenic Risk for Major Depressive Disorder	***r = -.45, p = .008***	***r = .44, p = .016***

Table 5.24 – Correlational Analysis (Controlling for CNT): Polygenic Risk for Major Depressive Disorder - Control Participants (N=34)

For all correlations, *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$.

5.9 Discussion

5.9.1 Neuropsychological Measures

Overall, results were as expected and in line with hypotheses, with the combined patients group underperforming in all cognitive domains compared to control participants. Individuals with schizophrenia scored lower than those with bipolar disorder in the majority of neuropsychological tasks and in turn, patients with bipolar disorder scored lower than control participants. To reduce the risk of Type II errors, significant *p*-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq .05$. As it is possible some results could be attributable to the effects of medication, association analysis was conducted which did not identify any significant association between antipsychotics (CPZ equivalent) and any neuropsychological measure. Although association analysis was conducted and there were no significant differences identified between medication and patient groups, CPZ equivalents were not included as covariates which may have limited these findings. This is an important consideration for future work, especially in view of the fact that medication, particularly first generation antipsychotics such as chlorpromazine, can result in movement disorders, including Parkinsonism, which could confound measures utilising fine motor function (D Thomas & Dauner, 1992; Owens, D.C. 2014).

5.9.2 General Intelligence

In line with hypotheses, current IQ for the combined patients group (schizophrenia and bipolar disorder) was significantly reduced compared to control participants, as was IQ difference, i.e. the difference between premorbid and current IQ.

Prior to controlling for variables known to impact on cognitive function (current IQ, age and gender), test results for the main group comparisons as well as for additional exploratory analyses were significantly lower in patients compared to controls across all neuropsychological measures. As previously, it should be noted that antipsychotic medication may have played a part in these results and CPZ equivalents should be included as covariates in future work.

This is also in line with hypotheses, as constructs such as reasoning and problem solving, attention, memory and processing speed highly correlate with general intelligence (Kahn & Keefe, 2013).

Comparing schizophrenia and bipolar disorder groups separately, current IQ was lower in individuals with schizophrenia than those with bipolar disorder, however a direct comparison did not reach significance. This was unexpected as cognition is known to be most impaired in schizophrenia, however, five individuals from the schizophrenia sample were first episode psychosis cases which may have contributed to minimising the overall deficit, as the IQ measure for these individuals was captured prior to them experiencing any ongoing cognitive decline which may occur as the illness progresses (Johnstone et al., 2010). Additionally, this result may be sensitive to environmental factors such as years of education, as the majority of individuals with schizophrenia in this sample had completed 'post-secondary education' (N=18) with a further 6 completing 'more than compulsory education' compared to 8 who completed 'compulsory education'. Palmer (1997) reported that 27% of all schizophrenia patients wouldn't be classed as cognitively impaired by clinical neuropsychological assessment (also applies to the general population = 85%). This is believed to be as a result of these individuals having higher premorbid functioning.

Although their performance would not warrant them being classed as impaired, it would, however, still be much lower than would have been expected based on their premorbid function and their parents level of education (Palmer et al., 1997).

In the bipolar disorder sample, 8 individuals had completed 'post-secondary education', 4 had completed 'more than compulsory education' and 4 completed 'compulsory education'.

Overall, IQ is impaired in the schizophrenia sample, however years of education, parents' education and higher premorbid functioning may help to account for the non-significant difference in current IQ between the schizophrenia and bipolar disorder patient groups.

IQ Difference, i.e. the difference between premorbid and current IQ was reduced (although not significantly) in both the schizophrenia (-6.38) and bipolar disorder (-7.13) samples. As can be seen however, the greatest reduction between premorbid to current IQ was identified for individuals with bipolar disorder. This was again an unexpected result, as IQ is generally preserved in bipolar disorder (Lewandowski et al., 2011). As with the unexpected result for current IQ, this difference may be accounted for by the five first-episode psychosis cases in the schizophrenia sample and the fact that there were two particularly impaired individuals in the bipolar disorder sample, both of whom had >30 points difference between measures of their premorbid and current IQ. Also of note is the fact that the bipolar disorder sample were older (M=44 years) than the schizophrenia sample (M=38 years) and that as a group, the bipolar disorder sample had high polygenic risk profile scores for bipolar disorder, possibly making them an especially 'genetic' or developmental group.

Overall, these results support the literature which has consistently reported impaired general intelligence in schizophrenia (Aylward et al., 1984; Heinrichs et al., 1998; Johnstone et al., 1999; Caspi et al., 2003; McIntosh et al., 2005; Osler et al., 2007; Woodberry et al., 2008; Joyce et al., 2013).

Global impairments in IQ have been reported to pre-date psychosis onset, and studies have also reported significantly poorer performances in tasks assessing general intelligence in people who later develop schizophrenia as far back as primary school (Caspi et al., 2003, Osler et al., 2007).

General intelligence is strongly genetic and highly heritable (McIntosh et al., 2005; Toulopoulou et al., 2007; Deary et al., 2009) although no single genetic locus has as yet been identified as being unequivocally associated with intelligence (Deary et al., 2009). Cognitive ability has, however, been reported as being a true endophenotype for susceptibility to schizophrenia (Lencz et al., 2014) and as such, warrants further investigation - especially with regard to identifying the genes associated with intelligence and it's high heritability.

Associations have been found between certain genes and measures of cognitive ability, in particular, older healthy females carrying the Cys allele from the *DISC1* gene were found to have poorer cognitive ability in old age (Thomson et al., 2005).

IQ generally remains intact in bipolar disorder, at least until the experience of a first episode of illness, and levels of impairment are not as severe as those seen in schizophrenia, however impaired cognition is a core feature of the illness (Bora et al., 2009).

It is also now becoming more evident that general cognitive ability does not necessarily return to premorbid levels during periods of euthymia as previously believed, and that individuals with bipolar disorder continue to suffer cognitive impairment during all phases of the illness as a result of residual symptoms of hypomania and/or depression (Angst & Sellaro, 2000; Thompson et al., 2005; Kurtz & Gerraty., 2009; Bora et al., 2010). At the time of testing, this sample were assessed as euthymic, however it is evident from the results that their current IQ is lower than their premorbid IQ which supports the fact that cognitive impairment is still present.

5.9.3 Attention and Processing Speed

From the Brief Assessment of Cognition in Schizophrenia (BACS) and the Cambridge Neuropsychological Test Automated Battery (CANTAB), main group comparisons and additional exploratory analyses identified significant differences in all cognitive domains. Three measures of attention and/or processing speed were robust controlling for current IQ, age and gender. Significantly reduced performances were identified in the combined patients group compared to control participants for motor speed and attention and processing speed (from the BACS) and five-choice reaction time (from the CANTAB).

These results are in line with the hypotheses and also support previous findings in which processing speed produced the largest group difference effect size in a meta-analysis between patients with schizophrenia and control groups in a large battery of neuropsychological assessments (Dickinson et al., 2007). A study by McIntosh et al., (2005) found evidence that genetic liability to schizophrenia was related to intellectual abnormalities including psychomotor performance and that all patient groups were significantly impaired compared to controls.

Patients with schizophrenia and/or bipolar disorder, as well as their non-affected family members were also found to be impaired on measures of psychomotor performance. In a later study, Glahn et al., (2010) postulated information processing speed as being a candidate endophenotype for bipolar disorder and suggested it could be one of the main causes of cognitive impairment in both schizophrenia and bipolar disorder.

Looking specifically at patient groups, a significant difference was identified, after controlling for current IQ, age and gender, for motor speed as assessed by the token motor task from the BACS.

These findings could be attributable to the effect of medication, as at the time of testing, 29 of 32 patients with schizophrenia and 7 of 16 patients with bipolar disorder were receiving antipsychotics. To minimise this possibility, correlational analysis was conducted between antipsychotic dose (CPZ Equivalent) (Gardner et al., 2014) and each neuropsychological assessment with no significant results. CPZ equivalents were also directly compared between patient groups, again with no significant results. Although medication effects were considered, future work would benefit by including CPZ equivalents as covariates in the main analysis, particularly when investigating measures utilising fine motor function. This is especially important with first generation antipsychotics such as chlorpromazine, which commonly produce extrapyramidal symptoms as side effects, including Parkinsonism (D Thomas & Dauner, 1992; Owens, D.C. 2014).

These findings support hypotheses with poorer performances from individuals with schizophrenia compared to those with bipolar disorder.

Results are also in line with previous findings which have reported impaired attention and processing speed in both schizophrenia and bipolar disorder (Fleming et al., 2004; McIntosh et al., 2005; Dickinson et al., 2007; Glahn et al., 2010; Lewandowski et al., 2011; Joyce, 2013) with the greatest deficits identified in schizophrenia.

No group differences were identified between individuals with schizophrenia and individuals with bipolar disorder for either of the simple or five-choice reaction time tasks which is in keeping with rationale 1 and further suggests that the earlier reported *DISC1* effect identified between family translocation carriers and non-carriers is an effect of the translocation.

5.9.4 Symptom Severity and Neuropsychological Measures

Symptom severity, particularly positive and negative symptoms, were hypothesised to be significantly associated with neuropsychology - particularly general intelligence (IQ) and measures of processing speed.

In line with hypotheses, negative symptoms - as measured by both the Positive and Negative Symptoms Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) - were significantly associated with general intelligence (current IQ) in the schizophrenia sample; bipolar disorder sample and with both patient groups combined. These results support previous findings in which negative symptoms were reported as being significantly associated with impaired general intellectual ability (IQ) in both schizophrenia and bipolar disorder (Andreasen et al., 1990; Addington et al., 1991; Strauss, 1993; Berman et al., 1997; Basso et al., 1998; Nieuwenstein et al., 2001; de Gracia Dominguez et al., 2009; Leeson et al., 2009; Bowie et al., 2010; Lewandowski et al., 2011).

As no study investigated general intelligence (current IQ) as a specific outcome measure, results could not be directly compared with previously reported findings. Overall however, as general intelligence is measured from the summed performances from a variety of tasks tapping a number of specific cognitive domains, i.e. memory, attention and processing speed, executive function etc., results from this study are in support of previous findings.

Studies investigating clinical symptoms and cognitive function in both schizophrenia and bipolar disorder include Krishnadas et al., (2014) who reported that residual negative symptoms (as measured by the SANS) mediated a difference in the cognitive performance of those with schizophrenia and those with bipolar disorder. In line with the results from this study, both of their patient groups performed worse than healthy controls.

General psychotic symptoms and antipsychotic medication were investigated, however neither of these explained this relationship. A limitation of this study is that a measure of premorbid IQ was not gathered which may have been able to help explain differences in cognitive performance and is a consideration for future work.

Studies investigating measures of processing speed have reported mixed findings. A visual backward-masking study by Braff (1989) reported impaired visual identification thresholds in schizophrenic patients with negative and/or mixed symptomology compared to patients with positive symptomology and healthy control participants. Following these findings, Strauss (1993) posited that positive and negative symptoms represented different underlying processes, with positive symptoms more related to auditory processing deficits and negative symptoms more related to visual and/or motor impairments. Buchanan et al., (1997) focussed on schizophrenia and negative symptomology. Their participants were split into two groups - those with and those without the deficit syndrome (negative symptoms).

Participants undertook the Continuous Performance Test (CPT) and the study reported finding attentional impairments in those with the deficit syndrome but not in those without.

Cornblatt et al., (1997) failed to find a significant relationship between attention using the CPT and either positive or negative symptomology. Their study went on to suggest that attention and clinical symptoms were independent and remained independent even after illness onset.

In 2001, Nieuwenstein et al., undertook a meta-analysis of CPT and Wisconsin Card Sorting Task (WCST) studies to investigate the relationship between neurocognitive functioning and symptom dimensions in schizophrenia and reported a significant relationship between negative symptoms and poorer performances on both the CPT and the WCST.

A further meta-analysis conducted by Cohen et al., (2007) investigated the neuropsychology of the deficit syndrome in schizophrenia and reported that patients with the deficit syndrome (negative symptoms) were globally more neuropsychologically impaired than patients without the deficit syndrome.

A recurring limitation in the majority of these studies is the effect of antipsychotic medication on task performance. Medication effects were considered from an improvement/recovery perspective in one study (Cornblatt et al., 1997) but were not accounted for in any study which may have impacted on the reported results. In the meta-analyses the authors reported that most of the included studies did not find significant group differences between these variables and therefore determined that the impact of these, if any, would be relatively small. Nonetheless, antipsychotics commonly produce extrapyramidal symptoms including Parkinsonism which can negatively impact fine motor function (D Thomas & Dauner, 1992; Owens, D.C. 2014).

Fine motor function is required for the successful completion of a number of neuropsychological tasks including the CPT, therefore fully investigating medication effects is an important issue to consider.

Negative symptoms are known to correlate in severity with impaired cognition in cross-sectional assessments and the severity of cognitive impairment and negative symptoms are known to be accurate predictors of real-world functional outcome, so much so that if negative symptoms are experienced early into illness, the outcome would be expected to be much worse (Harvey et al., 2005). It is also known that negative symptoms can be extremely debilitating and their management has proved to be challenging, however negative symptoms are now considered as being a separate dimension of psychopathology rather than as a neurochemical or structural abnormality (Mitra et al., 2016).

From this study, general intellectual ability (current IQ) was found to be significantly associated with negative symptoms, supporting the hypotheses and concurring with the wider literature. Future work investigating negative symptoms and specific cognitive domains may lead to the identification of new treatment targets, improved management and ultimately improved functional outcome.

5.9.5 Polygenic Risk Profile Scores

In line with hypotheses, polygenic risk for schizophrenia was greater in patients (schizophrenia and bipolar disorder together) than control participants with analyses reaching the significance threshold. All analyses controlled for CNT (the number of non-missing SNPs used for scoring). Schizophrenia is highly heritable (Harrison & Owen, 2003; O'Donovan et al., 2009) and genetic risk for the later development of schizophrenia is believed to be conferred by a large number of alleles – some of which are common alleles which have a small effect (Ripke et al., 2014). It has also been suggested that as much as a half to one third of the genetic risk of schizophrenia is linked by common alleles (Ripke et al., 2014). The result from this study was fairly weak ($p = .05$), however this may be due to the small sample size (schizophrenia N=25, bipolar disorder N=16, control participants N=34). Overall these results are in line with the literature and the view from The International Schizophrenia Consortium (2009) that there is a substantial polygenic component – made from thousands of common alleles of very small effect - which increases the risk of schizophrenia (Purcell et al., 2009).

No differences were identified for either polygenic risk for bipolar disorder or polygenic risk for major depressive disorder between the combined patients' group and control participants. However when investigating patients by diagnosis, although not significant, there was a greater genetic loading for polygenic risk for schizophrenia within the bipolar disorder sample than the schizophrenia sample which was an unexpected finding. This may be accounted for by the fact that the schizophrenia sample included first episode cases, some of whom may since have received a diagnosis of bipolar disorder and further, as is the nature of psychiatric nosology, some original schizophrenia diagnoses may have changed over the course of this study.

Polygenic risk for bipolar disorder was found to be significantly higher in those with bipolar disorder compared to those with schizophrenia as well as between the bipolar disorder sample and control participants which is in the expected direction.

5.9.6 Polygenic Risk Profile Scores and Neuropsychological Measures – Combined Patients Group

Prior to controlling for CNT, polygenic risk for schizophrenia was found to be significantly associated with premorbid to current IQ difference in the combined patients group. Measuring the difference between an individuals estimated premorbid IQ and their current IQ is useful because although poor cognitive function is known to be a key symptom of major mental illness - particularly in schizophrenia - we are able to quantify the extent to which general intelligence has reduced (or not) on an individual basis. Although not significant, polygenic risk for schizophrenia was also found to be weakly associated with current IQ as well as verbal fluency.

These results are in general supportive of previous findings that suggest polygenic risk for schizophrenia is associated with lower general intelligence, for example, Lencz et al., (2014) provided molecular genetic evidence of an overlap between risk for schizophrenia and cognitive ability. Their large study reported that individuals with schizophrenia had lower cognitive polygenic scores than control participants and that polygenic risk for schizophrenia was significantly associated with lower general cognitive performance. An earlier study by Davies et al., (2011), was the first study to show biologically that human intelligence is highly polygenic and they also reported that intelligence could be predicted using genetic (SNP) information (single nucleotide polymorphism).

The combined patients group also revealed a number of associations between polygenic risk for major depressive disorder and several cognitive assessments including premorbid to current IQ difference, motor speed, verbal fluency and a measure of executive function. To our knowledge, this is the first report of a relationship between polygenic risk for major depressive disorder and measures of neuro- cognition. Very recently, a large mixed model study by Liebers et al., (2016) failed to find any significant relationships between polygenic risk for major depressive disorder and any cognitive measure in a sample of healthy older adults.

Although not an observable behavioural study, a significant relationship was previously reported between polygenic risk for major depressive disorder and reduced white matter integrity in the superior longitudinal fasciculus (SLF) (Whalley et al., 2013). This region is believed to be involved in a number of higher-order cognitive functions including memory, motor function and attention (Whalley et al., 2013; Makris et al., 2005), and may relate to a range of cognitive deficits often seen in patients as well as unaffected family members who carry more common, risk-associated genetic variants for major depressive disorder.

5.9.7 Polygenic Risk Profile Scores and Neuropsychological Measures – Patients by Diagnosis and Control Participants

Looking at the schizophrenia sample, no significant associations were identified between measures of cognition and any of the polygenic risk profile scores which was contrary to hypotheses. These results disagree with positive findings reported between general intelligence and polygenic risk for schizophrenia (Lencz et al., 2014; McIntosh et al., 2013; Davies et al., 2011; Hubbard et al., 2015), however studies by Fowler et al., (2012) and van Scheltinga et al., (2013) also resulted in non-significant associations between polygenic risk for schizophrenia and general intelligence.

The negative results here could be due to sample size as the significant associations were detected in much larger studies, more likely to be able to detect effects.

Significant relationships were identified in the bipolar disorder sample between polygenic risk for schizophrenia and both current IQ and premorbid to current IQ difference. These results are in line with hypotheses and support previous findings which suggest that higher polygenic risk for schizophrenia is related to lower general cognitive ability over the lifespan (McIntosh et al., 2013).

Increased polygenic risk for schizophrenia has also been reported as being able to predict fluctuations in neurocognition in the general population (Hatzimanolis et al., 2015).

Significant associations were also identified in the bipolar disorder sample between polygenic risk for bipolar disorder and both current IQ and premorbid to current IQ difference.

Polygenic risk for major depressive disorder, however, was found to significantly associate with current IQ, premorbid to current IQ difference, five-choice reaction time and motor speed which was an unexpected finding. As part of additional exploratory analyses, verbal memory, verbal fluency and executive function were also found to be significantly associated with polygenic risk for major depressive disorder. These results are in line with the previously reported results from the combined patients group which also found the majority of significant relationships between measures of neuropsychology and polygenic risk for major depressive disorder.

For control participants, no significant associations were identified between any cognitive assessments and either polygenic risk for schizophrenia or polygenic risk for bipolar disorder.

Polygenic risk for major depressive disorder however, was significantly associated with attention and processing speed which is in disagreement with the findings from a study by Liebers et al., (2016) who found no association between cognition and polygenic risk for major depression, however this result does appear to be in line with the findings already reported from this study.

Research to identify depression genes has so far failed to identify any genome-wide significant SNPs, however recent work by de Moor et al., (2015) reported a genome-wide significant SNP located at a novel locus on 3p14 located in $MAGI_1$ which was found to significantly predict neuroticism as well as major depressive disorder.

This gene has previously been associated with schizophrenia, bipolar disorder and episodicity in major depressive disorder (de Moor et al., 2015) and may prove to be fruitful for future work.

In this study, polygenic risk for major depressive disorder has been found to correlate with impaired IQ and slowed reaction time in patients who are not currently depressed, suggesting there may be genetic risk markers in this population which are impacting on cognition. This is a novel finding as there is currently no precedent in the literature. These results are not likely to be attributable to the effects of medication and suggest there may be a biological component related to the genetics of depression.

5.9.8 Polygenic Risk Profile Scores: Symptom Severity and Self-Report Questionnaire Data – Combined Patients Group

Polygenic risk profile scores were investigated with clinical symptoms - in particular positive and negative symptomology – and additional exploratory analysis investigated data from self-report mood questionnaires.

Polygenic risk for bipolar disorder was significantly related to self-reported mania in the combined patients group and polygenic risk for major depressive disorder was found to be significantly associated with paranoid ideation as measured by the Kings Schizotypy Questionnaire (KSQ).

5.9.9 Polygenic Risk Profile Scores: Symptom Severity and Self-Report Questionnaire Data – Patients by Diagnosis and Control Participants

Investigating patients by diagnosis revealed a significant relationship between psychoticism as measured by the Eysenck Personality Questionnaire (EPQ) and polygenic risk for major depressive disorder in the schizophrenia sample.

Polygenic risk for major depressive disorder was also found to be significantly associated with negative symptoms as measured by both the PANSS and the SANS in the bipolar disorder sample.

A number of interesting relationships were identified in the control sample. Recurrent illusions, a measure captured by the KSQ, was found to be significantly associated with all three polygenic risk profile scores.

Magical thinking - also measured by the KSQ - was significantly associated with polygenic risk for schizophrenia, and although non-significant, magical thinking was also found to be weakly associated with polygenic risk for major depressive disorder.

A search of the literature failed to identify any studies that investigated polygenic risk with either clinical symptoms or self-reported personality/mood data, therefore we were unable to compare these results.

Looking at the individual polygenic risk profile scores in participants who reported experiencing recurrent illusions and magical thinking suggests that increasing polygenic risk for major psychiatric disorder (schizophrenia, bipolar disorder and major depressive disorder) in general is associated with an increased risk of the experience of schizotypal symptoms, in particular recurrent illusions and magical thinking. Schizotypy is more commonly identified in family members of probands with schizophrenia who have been found to have higher schizotypal scores than controls without a family history of schizophrenia (Heron et al., 2003). Although it is not uncommon for control participants to report experiencing various schizotypal symptoms, it is interesting that significant associations between these ratings and polygenic risk were only identified in the control sample.

5.9.10 Limitations

It is acknowledged that when designing a research study, a power calculation should be performed to determine an appropriate sample size. Power calculations allow researchers to establish the minimum number of participants they will need to recruit to obtain sufficient power for their study (which is usually 80%) (Cohen, J. 1992).

Power calculations also help to prevent time wasting and help to save money by identifying studies that are potentially underpowered. Power calculations can also prevent too many participants from being recruited (Whitley & Ball, 2002). Retrospectively, a power calculation should have been performed for this study, however as discussed previously, due to the nature of the *DISC1* family, it was necessary to recruit as many family members as possible and therefore a power calculation wasn't performed. For the patient and control groups, sample sizes were higher than the *DISC1* kindred, having a combined patients group of n = 48 and a control group of n = 42 which is similar or higher than comparative studies and as such, any effect would hopefully be similar, if not greater without running an actual power analysis.

It is also acknowledged that the patient cases recruited for this study included schizophrenia and bipolar disorder only, however this may not have been the best mix of psychiatric diagnoses as there are a wide range of diagnoses in the *t*(1;11) kindred. Diagnoses include schizophrenia, bipolar disorder, schizoaffective disorder, recurrent major depressive disorder, single episode depression, cyclothymia and adult conduct disorder therefore including patients with major depressive disorder would have been very beneficial and is a consideration for future work.

As previously mentioned, a further limitation concerns medication. 29 out of 32 schizophrenia cases and 8 out of 16 bipolar disorder cases were taking antipsychotic medication. Combining the various types of antipsychotic medications and their varying doses as chlorpromazine equivalents provides a very useful way to examine antipsychotic medications together (Gardner et al., 2010). Direct comparisons were conducted between medication and patient groups with no significant results. Correlational analyses were also conducted to look for any significant relationships between medication and any of the clinical or cognitive measures again with no significant results.

As a result of these preliminary analyses, chlorpromazine equivalents were not included as a covariate which in hindsight may have limited the results. As such, chlorpromazine equivalent values should be included as a co-variate in any future work to ensure all potential confounding factors are controlled for. This is particularly important when investigating measures that rely on fine motor function in view of the commonly produced extrapyramidal symptoms as side effects, specifically movement disorders such as Parkinsonism.

An unexpected limitation concerns the patient and control participants themselves, as they may not be as representative of these samples as originally intended. Schizophrenic cases appear to be relatively cognitively intact which may be as a result of greater premorbid function and greater number of years of education/parent's education. The majority of schizophrenic cases were recruited locally from outpatient clinics and from the case loads of psychiatrists at the Royal Edinburgh Hospital and they were happy to take part in research, having participated in previous studies. The bipolar disorder sample was surprisingly genetic and a number of unaffected control participants reported they had experienced schizotypal symptoms. A number of control participants had also previously suffered from depression, however this is in line with the prevalence of depression expected in Scotland's general population (Fernandez-Pujals et al., 2015).

5.9.11 Summary

This is one of the first studies to relate cognition and clinical symptomology to polygenic risk profile scores and is also the first study to compare the cognitive and/or clinical effects of having a psychiatric illness in general to the cognitive and/or clinical effects of the *t*(1;11) balanced translocation within the *DISC1* family without the need for direct statistical comparisons between the family, patient and/or control groups.

Schizophrenia and bipolar disorder cases were compared using standardised measures as provided by the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2008) of which to date only four studies could be found (Cholet et al., 2014; Caletti et al., 2013; Kuswanto et al., 2013; Hill et al., 2013). Three of these studies reported robust deficits in cognitive function with the greatest cognitive impairment seen in schizophrenia cases, followed – where investigated - on a continuum by depressed schizoaffective, manic schizoaffective, psychotic bipolar disorder and bipolar disorder. Verbal memory, together with attention and processing speed sub-scores were reported to be most severely impaired in schizophrenia, however one study (Kuswanto et al., 2013) reported no significant differences in cognitive performance between their schizophrenia and bipolar disorder samples, reporting that both patient groups suffered a similar degree of cognitive impairment.

Direct comparisons between schizophrenia and bipolar disorder samples in this study for the six tasks which make up the BACS identified significantly poorer performances from the schizophrenia sample for motor speed (as assessed by a token motor task) and although not significant, attention and processing speed (as assessed by a digit symbol coding task) marginally missed the significance threshold. These results are in line with previous findings using this test battery and provide support for the use of a standardised battery of neurocognitive tasks to allow the comparison of future studies assessing cognition in schizophrenia and bipolar disorder.

Cognitive impairment is known to be an important predictor of functional outcome (Kahn & Keefe, 2013) and has been found to correlate more with functional outcome than symptoms (Joyce, 2013), therefore lending itself as a potential treatment target.

This notion is gaining momentum, especially as psychological interventions are beginning to show that general cognition can be improved in schizophrenia (Joyce, 2013), making it a promising and important area for future work.

Polygenic risk for schizophrenia (PGRS) was, as expected, significantly greater for the combined patients group compared to control participants and PGRS was also significantly associated with measures of neuropsychology in the bipolar disorder sample, particularly premorbid and current IQ. For control participants, PGRS was significantly associated with schizotypal symptomology, i.e. recurrent illusions and magical thinking – this is an interesting finding as it only occurred in control participants suggesting increased polygenic risk for major mental illness in general increases the risk of experiencing schizotypal symptoms.

Polygenic risk for bipolar disorder (PGRBD) was significantly greater in bipolar disorder cases than schizophrenia or control samples and PGRBD was significantly associated with both current IQ and premorbid to current IQ difference in the bipolar disorder sample.

Self-reported measures of personality, together with self-reported and clinically rated measures of mood – particularly negative symptoms - were found to significantly associate with polygenic risk. A search of the literature failed to find any similar studies, therefore results could not be compared.

Negative symptomology has consistently shown strong correlations with neuropsychological dysfunction and is known to be a strong outcome predictor making it a logical target for treatment, however future work may also benefit from investigating polygenic risk and clinical symptoms.

Polygenic risk for major depressive disorder (PGRMDD) produced the largest number of associations with measures of neurocognition, clinical symptomology and self-reported measures of personality. In the combined patients group, PGRMDD was significantly associated with premorbid to current IQ difference, motor speed, verbal fluency and executive function, while PGRMDD was found to be significantly associated with current IQ, premorbid to current IQ difference, five-choice reaction time and motor speed in the bipolar disorder sample and with attention and processing speed in the control sample.

Impaired attention and/or measures of processing speed may be pre-existing risk markers for the later development of major depressive disorder (Sarapas et al., 2012) and may have a biological link to PGRMDD which has been found to be significantly related to measures of attention and processing speed across all groups and as such, warrants further investigation.

These novel findings could be accounted for by the fact that schizophrenia, bipolar disorder and major depressive disorder are believed to share genetic architecture, therefore future studies could potentially glean more information by creating a cross-disorder polygenic risk profile score.

Chapter 6: Synthesis

6. Synthesis

This chapter provides a summary of the aims and key results from this thesis together with discussions in relation to the implications of these findings, evidence for and against the *DISC1* gene and the *t*(1;11) balanced translocation, strengths and limitations of the study, considerations for future work and final conclusions.

6.1 Summary of Aims

The primary aims of this thesis were to compare the cognitive, clinical and polygenic profiles of family members with and without psychosis to establish the effect, if any, of a rare genetic abnormality, believed to increase the risk of major mental illness; the *DISC1 t*(1;11) balanced translocation. Following the results from previous work, it was firstly hypothesised that general intelligence and measures of processing speed would be significantly reduced in *t*(1;11) carriers compared to non-carriers. It was also hypothesised that clinical symptoms, in particular positive and negative symptomology, would be significantly related to neurocognition in *t*(1;11) carriers and finally, it was hypothesised that polygenic risk for schizophrenia would be significantly related to measures of cognition as well as clinical symptomology, particularly positive and negative symptoms in *t*(1;11) carriers.

Parallel investigations were conducted between participants with schizophrenia, bipolar disorder and unaffected controls. These samples were recruited to facilitate the comparison of the effect of having a major psychiatric disorder in general, to the effect of having the *t*(1;11) translocation without the need for direct statistical analyses. Direct comparisons were not conducted between the *t*(1;11) kindred and patients primarily due to the potential problem of confounders such as shared heredity, age and gender as well as a number of environmental factors including geographical location, education and socio-economic status (see 6.6).

6.2 Summary of Results: *t*(1;11) Carriers and Non-Carriers

As seen in the narrative literature review (Chapter 2), a number of studies have investigated *DISC1* and cognition, but few specifically investigated general intelligence as an outcome measure. Most studies gathered a measure of either premorbid or current I.Q. however unfortunately, these data were not comparable due to the variety of methodologies employed. Blackwood et al., (2001) reported premorbid I.Q. to be within the normal range in a number of family members from the *t*(1;11) kindred, and it can now be seen from these results that general intelligence (current IQ), is particularly impaired in *t*(1;11) carriers compared to non-carriers. This could, of course, be as a result of medication, although correlation analysis did not identify any significant associations between general intelligence and CPZ equivalent (antipsychotic medication). Three *t*(1;11) carriers were also receiving sodium valproate which has been reported as having a negative impact on verbal intelligence (Haddad et al., 2009), however the points difference in the most impaired *t*(1;11) case is circa 32 which is unlikely to be the result of valproate alone.

These results support an effect of the *DISC1* gene firstly by increasing the risk for the later development of a major psychiatric disorder by negatively impacting on general intelligence developmentally, and secondly, those who carry the rare genetic risk factor (*DISC1 t*(1;11) balanced translocation) could be subjected to a 'double hit' on their general intellectual ability as not only will their intelligence already have been compromised developmentally, the later development of a major mental disorder brings with it the potential of experiencing psychosis which, it is known, can result in a further insult on intelligence.

Studies investigating *DISC1* and neuropsychology have proved inconclusive.

The majority of studies measuring aspects of cognitive function have been genetic in nature, designed to identify relationships between relatively common single nucleotide polymorphisms (SNPs) or haplotypes with specific cognitive domains. As concluded in Chapter 2, *DISC1*/*DISC1* SNPs and/or *DISC1* (*DISC1/TRAX*) haplotypes have shown association with a number of cognitive domains, the majority of which utilise a working memory component, supporting the neurodevelopmental hypothesis of schizophrenia (Owen et al., 2011). Impaired working memory is likely to have a knock-on effect on other cognitive processes, which in turn, are likely to have a negative impact on measures of general intelligence (I.Q.).

Reaction time and, in particular, attention and processing speed were consistently found to be significantly reduced in this study, which supports the earlier auditory P300 ERP findings reported by Blackwood et al., (2001). In addition to the abnormal P300 findings, these results are also in general support of a number of other studies investigating *DISC1* and measures of cognition including Burdick et al., (2005) in which *DISC1* SNPs were associated with a rapid visual search task. Visual attention has also previously been reported to associate with a *DISC1* haplotype (HEP3) (Hennah et al., 2005) and Liu et al., (2006) reported an association between *DISC1* and impaired sustained attention.

Cannon et al., (2005) reported an association between visual reaction time and a rare 4-SNP *DISC1/TRAX* haplotype ('AATG') and Palo and colleagues reported an association between category fluency and a common *DISC1* SNP, namely Ser704Cys (rs821616). A further association was identified in their study with psychomotor processing speed and the *DISC1* SNP, rs980989. More recently, Nicodemus and colleagues (2014) examined category fluency using a novel computational linguistic approach which they reported as being negatively associated with the *DISC1* SNP, rs12133766.

It can be seen from this study that the *DISC1 t*(1;11) translocation appears to impact upon general intelligence and attention and processing speed which are significantly reduced in family translocation carriers. These results support all earlier findings, however as it is known that the *DISC1 t*(1;11) translocation reduces *DISC1* protein expression in carriers by approximately 50% (Miller et al., 2005), it was not considered appropriate to investigate measures of cognition with SNP status. The marked reductions evidenced in all cognitive tasks, however, supports an effect of the *t*(1;11) balanced translocation and therefore the *DISC1* gene, for increasing the risk of major mental illnesses, in particular schizophrenia, bipolar disorder and major depressive disorder.

6.3 Summary of Results: Patients and Unaffected Control Participants

Significant cognitive deficits were evident across all tasks between patients (combined patients group) and unaffected control participants and a similar pattern of cognitive impairment was seen between schizophrenia and bipolar disorder samples. These results are in line with the literature and although a significant difference was not identified between individuals with schizophrenia and those with bipolar disorder for general intelligence (current IQ), it could be seen that IQ for the schizophrenia sample was most impaired and was lower than in those with bipolar disorder which, in turn, was lower than unaffected control participants. It was also noted that the patient samples recruited for this study may not be representative in that the majority of individuals with schizophrenia had completed more years of full-time education and had better socio-economic backgrounds than most which will be revisited in section 6.6.

A significant difference was identified for psychomotor speed using a token motor task and although not significant, a digit symbol coding task to measure attention and processing speed marginally missed the significance threshold. Individuals with schizophrenia demonstrated poorer performances for both of these tasks which is as expected and in line with the literature.

This is one of the first studies to relate polygenic risk to measures of neuropsychology and of particular interest is the finding that polygenic risk for major depressive disorder was found to significantly correlate with impaired IQ and slowed reaction time in patients who were not currently depressed. This suggests there may be genetic risk markers in this population which are impacting on cognition. This is a novel finding. These results are not likely to be attributable to the effects of medication and suggest this IQ effect may be one biological component related to the genetics of depression.

Measures of information processing were found to be significantly related to polygenic risk for major depressive disorder in both patient groups as well as with healthy control participants suggesting that polygenic risk for major depressive disorder may be a risk factor for impaired processing speed as well as the later development of major psychiatric disorder. Efficient information processing has been reported as being a "*prerequisite of higher cognitive abilities*" and is robustly associated with intelligence (Jensen, A. R. 2006).

Research has also proposed that processing speed is associated with white matter integrity and polygenic risk for major depressive disorder has also been found to be significantly associated with reduced white matter integrity in individuals at high risk of mood disorder (Whalley et al., 2015). Polygenic risk for major depressive disorder has also been significantly associated with variability in amygdala-medial prefrontal circuitry, and found to be significantly associated with impaired social functioning (Holmes et al., 2013).

Further research examining polygenic risk for major depressive disorder with cognitive function and related brain regions may help to guide future research.

6.4 Observational Comparison of Results Between *t*(1;11) Kindred, Schizophrenia and Bipolar Disorder Cases

General intelligence (current IQ) was found to be particularly impaired in *t*(1;11) carriers with psychotic disorder (M = 67, SD = 6.2) compared to patients with schizophrenia (M = 103, SD = 16.7) and bipolar disorder (M = 105, SD = 18.9). This observation supports the earlier reported family results for an effect of the *DISC1* balanced translocation having a negative developmental impact on intelligence. These findings could also, however, be the result of the effect of medication, as 29 of the 32 schizophrenia cases and 8 of the 16 bipolar disorder cases were receiving antipsychotic medication. Although direct comparisons and correlational analyses did not identify any significant associations between general intelligence and antipsychotic medication (CPZ equivalent), sodium valproate has also been reported to have a negative impact on verbal intelligence (Haddad et al., 2009) which may have had an effect on these results. Taking this into consideration, the most cognitively impaired *t*(1;11) case had an I.Q. points difference of circa 32 which is unlikely to be the result of valproate alone. Overall, the indirect comparison of general intellectual ability between the *DISC1 t*(1;11) carriers with psychotic disorder and both patient groups supports an effect of the *DISC1 t*(1;11) balanced translocation negatively impacting on intelligence.

Measures of processing speed were also found to be impaired - more so than the level of impairment evident in patients with schizophrenia. It was interesting to note that contrary to the family results, no group effect was evident for patients' reaction time tasks, suggesting the *DISC1* effect seen within the family results is an effect of the *t*(1;11) translocation.

These results are also in line with recently published imaging findings from a parallel study which reported that the *t*(1;11) translocation was significantly associated with reduced white matter integrity in *t*(1;11) carriers (Whalley et al., 2015).

Polygenic risk for bipolar disorder was found to be significantly different between *DISC1* family members (*t*(1;11) carriers and non-carriers) as well as between patients (schizophrenia and bipolar disorder samples). As expected in the patients group, higher polygenic risk profile scores for bipolar disorder were evident in those with bipolar disorder.

Within the family, higher polygenic risk profile scores for bipolar disorder were evidenced in *t*(1;11) carriers, suggesting that *DISC1* may increase risk for major mental illness, in particular schizophrenia, bipolar disorder and major depressive disorder. It is worth noting that the patients included in the bipolar disorder sample in this study were found to be a particularly highly genetically loaded group and additionally, the majority of diagnoses within the *t*(1;11) family are affective in nature.

Polygenic risk for schizophrenia, although not significantly different, was higher in *t*(1;11) carriers than non-carriers and similarly in patients, polygenic risk for schizophrenia was also higher in cases of schizophrenia compared to bipolar disorder. These results also support a role for *DISC1* increasing the risk for major psychiatric illness and with reports that major psychiatric disorders, i.e. schizophrenia, bipolar disorder and major depressive disorder, have a shared genetic hierarchy (Craddock and Owen, 2010).

6.5 *DISC1* Challenges

There is a wealth of evidence in support of the *DISC1* gene and the *DISC1* pathway (Porteous et al., 2014). Additionally, recent work has also re-confirmed the importance of the *DISC1* *t*(1;11) balanced translocation (Whalley et al., 2015; Thomson, Duff et al., 2016) however, *DISC1* has not been without its' challenges – even the name 'disrupted-in-schizophrenia' has been suggested as being a 'misnomer' and 'prone to misinterpretation' (Sullivan et al., 2013).

One of the reasons this concern has arisen is because of the range of psychiatric diagnoses evident in the *DISC1* kindred which range from cyclothymia to schizophrenia. On the contrary, however, this phenotypic pleiotropy of the *t*(1;11) translocation is precisely what makes the *DISC1* kindred unique as it has been evident from the first report of the family. As such, the family have provided evidence for genetic and biological overlap between the major psychiatric disorders, i.e. schizophrenia, bipolar disorder and major depressive disorder (Smoller et al., 2013). Recent GWAS-derived estimates of co-heritability have estimated schizophrenia/bipolar disorder at 0.68; bipolar disorder/major depressive disorder at 0.47 and schizophrenia/major depressive disorder at 0.43 (Consortium C-D., 2013) and these estimates are entirely consistent with the spectrum of diagnoses seen in the *t*(1;11) family.

The relevance of the biology of *DISC1* to psychiatry and the wider significance of the original *t*(1;11) findings were also challenged (Sullivan et al., 2013). Their concern revolved around the fact that *DISC1* fell short in genome-wide association studies (GWAS) – the assumptions of which are based on the 'common disease; common variant' hypothesis, however *DISC1*, (and other rare variants such as *APP*, *PSEN1* and *PSEN2* in relation to Alzheimer's Disease) are all prime examples of the 'common disease; rare variant' hypothesis.

APP, *PSEN1* and *PSEN2* are all rare family-based variants which have provided important insights into Alzheimer's disease however, these would have been ignored had the GWAS criteria been applied (Porteous et al., 2014).

A further challenge surrounds investigating unique and rare variants and/or mutations in single families as they may ultimately be private to the particular family being studied and not to the disorder itself, therefore lacking generalisability. However, as mentioned above, single family studies have provided important insights into diseases such as Alzheimer's (Porteous et al., 2014). Whalley et al., (2015) have also posited that rare genetic family-specific variants such as the *DISC1 t*(1;11) balanced translocation could be especially useful by helping to explain the neurobiology of major psychiatric disorders such as schizophrenia as the result of a less complex genetic architecture within families and an increased penetrance at the endophenotype level. Investigating rare mutations and variants such as *DISC1* and the *DISC1 t*(1;11) balanced translocation offers an opportunity to help identify specific disease pathways mediated by *DISC1*, and the potential to identify and develop novel pharmacological treatment options which could ultimately, effectively reduce the symptoms of psychiatric disorders and greatly improve outcomes.

6.6 Limitations

Investigating the *DISC1 t*(1;11) balanced translocation was limited by the unavoidably low numbers of affected individuals and their non-translocation carrying relatives. With this in mind, being able to recruit a total of 26 family members (carriers N=13, non-carriers N=13), each of whom completed all measures required for this work, enabled the identification of a large effect of the *t*(1;11) translocation. This kindred are unique in nature and research opportunities with the family are rare. A full neuropsychological assessment has never been investigated or reported and the findings from this study are novel. These results provide evidence that the *t*(1;11) balanced translocation effects general intelligence and attention and processing speed. It is hoped that these important factors provide justification for this methodological limitation.

Another limitation concerns the investigation of a single family with a single-gene locus as although these studies provide important information about a particular group of psychoses and help to ascertain whether any such single-gene locus has a major effect on the risk of illness, it could well be the case that findings may only relate to that particular family and remain unique (Blackwood et al., 2001). In line with previous research by Blackwood et al., (2001) because of the rarity of the translocation it remains important to continue investigations with this family to identify any phenotypic differences between family members with and without the translocation, as well as between family members and unrelated individuals with major mental illnesses including schizophrenia, bipolar disorder and major depressive disorder which was the primary reason for recruiting a combined patients group.

A third limitation concerns medication status.

From the *t*(1;11) carriers, two individuals were taking antipsychotic medication together with a mood stabiliser, one individual was receiving a mood stabiliser only, and one was receiving an antidepressant only. From the patient groups, 29 out of 32 schizophrenia cases and 8 out of 16 bipolar disorder cases were taking antipsychotic medication.

Combining the various types of antipsychotic medications and their varying doses as chlorpromazine equivalents provides a very useful way to examine antipsychotic medications together (Gardner et al., 2010). Direct comparisons were conducted between medication and translocation status in the family and between patient groups with no significant results. Correlational analyses were also conducted to look for any significant relationships between medication and any of the clinical or cognitive measures. As a result of these preliminary analyses, chlorpromazine equivalents were not included as a covariate which in hindsight may have limited the results. Future work should consider including chlorpromazine equivalent values as co-variates to ensure all potential confounding factors are controlled for. This is particularly important when investigating measures that rely on fine motor function in view of the commonly produced extrapyramidal symptoms as side effects, specifically movement disorders such as Parkinsonism (Owens, D.C. 2014). A further consideration concerns the potential overlap between negative symptomology and the risk of adverse effects of antipsychotic medication. Although negative symptom ratings were low for the *DISC1* family (M = 9.6) and also for the patients group (M = 13.2) it should be noted that the benefits of antipsychotic medication in relieving the positive symptoms of psychosis can sometimes have negative consequences by way of adverse effects such as sedation and movement disorders which is another consideration for future work (Arango et al., 2004; Upthegrove, R. 2009; Muench et al., 2010).

Fourth – it is acknowledged that a power calculation was not performed as this wasn't deemed to be appropriate due to the unique nature of the family and the fact that the aim was to recruit as many family members as possible. It is acknowledged that when designing a research study, a power calculation should be performed to determine an appropriate sample size. Power calculations allow researchers to establish the minimum number of participants they will need to recruit to obtain sufficient power for their study (which is usually 80%). Power calculations also help to prevent time wasting and help to save money by identifying studies that are potentially underpowered and can also prevent too many participants from being recruited (Cohen, J. 1992; Whitley & Ball, 2002). Retrospectively, a power calculation should have been performed for this study, however as discussed previously, due to the nature of the *DISC1* family, it was necessary to recruit as many family members as possible and therefore a power calculation wasn't performed.

For the patient and control groups, sample size numbers were higher than those for the *DISC1* kindred, having a combined patients group of n = 48 and a control group of n = 42 which is similar or higher than comparative studies and as such, any effect would hopefully be similar, if not greater without running an actual power analysis.

Another statistical consideration is the presence of outliers. Outliers were not removed due to the low number of cases included in each analysis and they are shown in the main results, however analyses were conducted with the main outlier removed in which the result remained significant.

It has been noted that the family sample was limited by low numbers and as such, non-parametric tests were initially considered for the main analyses.

As the data were found to be normally distributed and the low sample size prevented the use of more rigorous statistical methods, parametric independent samples *t*-tests, Analysis of Variance (ANOVA) and Analysis of Covariance (ANCOVA) were considered to be the most appropriate. Non-parametric tests were used where homogeneity of variance was found to be violated and also for analysis of the self-reported personality and mood questionnaire data which were found to violate assumptions of normality.

A large number of analyses were conducted as part of the main *a priori* hypotheses and also as a result of additional exploratory analyses due to the fact that the family are so rare and opportunities to conduct investigations are limited. To reduce the chance of Type II errors, all analyses were corrected using the FDR procedure, however it is noted that some studies prefer not to correct for multiple comparisons due to the fact that mathematical corrections can substantially increase the risk of accepting the null hypothesis (K. J. Rothman, 1990). These calculations reduce the statistical power which in turn can lead to problems interpreting the study results therefore in this study, both uncorrected and corrected results are shown.

It has also been noted that the combined patients group, recruited to act as a 'positive control' group for the *t*(1;11) family, consisted of individuals with schizophrenia and bipolar disorder which, considering a number of family members have diagnoses of major depressive disorder, may not have been the best diagnostic split of psychiatric disorders. Diagnoses in the family include schizophrenia, bipolar disorder, schizoaffective disorder, recurrent major depressive disorder, single episode depression, cyclothymia and adult conduct disorder, therefore in hindsight, including patients with major depressive disorder would have been very beneficial and is a consideration for future work.

A further limitation was the decision not to conduct direct statistical comparisons between the family groups (*t*(1;11) carriers and non-carriers) and the patient groups (schizophrenia and bipolar disorder) and/or unaffected control participants. Research by Glahn et al., (2007b) has suggested that family members' brains are anatomically very similar and that certain areas are highly heritable. Shared heredity within the family would significantly confound any direct comparisons between these family members and a group of unrelated individuals, which is the main reason the patient groups and unaffected control participants were recruited. In addition to the shared heredity, other confounding factors include age, geographical location, socio-economic status, education and employment. Recruiting the patient and control groups allowed us to compare the effects of having a psychiatric illness in general to the effects of the *t*(1;11) translocation within the family without the need for direct statistical comparisons.

An unexpected limitation concerns the patient and control participants themselves, as they may not be as representative of these samples as originally intended. Schizophrenic cases appear to be relatively cognitively intact which may be as a result of greater premorbid function and greater number of years of education/parent's education. The majority of schizophrenic cases were recruited locally and were happy to participate in research, having taken part in previous studies. The bipolar disorder sample was surprisingly genetic and a number of unaffected control participants reported they had experienced schizotypal symptoms. A number of control participants had also previously suffered from depression, however this is in line with the prevalence of depression expected in Scotland's general population (Fernandez-Pujals et al., 2015).

Finally, not having a standardised battery of neuropsychological assessments prevents the comparison of results across studies which, if these were able to be compared, may identify new treatment targets.

6.7 Future Work

Going forward, future studies of the *t*(1;11) translocation could extend the findings from this study in the domains of attention and processing speed and general, especially fluid, intelligence. Being able to administer a non-verbal measure of IQ such as the Ravens Matrices (Raven, 1958) or the Culture Fair (Cattell, 1959) would provide a measure of current IQ not dependent on language based tasks.

The geographical locations of *t*(1;11) family members are particularly rural and not surprisingly, the majority of family members did not continue education beyond secondary school with the majority of occupation categories being either unemployed, manual or skilled manual.

Genetic studies may benefit from the creation of a cross-disorder polygenic risk profile score as it is becoming more and more evident that the major psychiatric disorders have a shared genetic hierarchy. A cross-disorder risk profile score could then be related to measures of neuropsychology within the family which may result in more robust findings.

Future work with patient groups would benefit from the continued investigation of polygenic risk with a particular focus on polygenic risk for major depressive disorder which to date has not been investigated as much as polygenic risk for schizophrenia or bipolar disorder. Relating polygenic risk for major depressive disorder to measures of neuropsychology may replicate the findings from this study and/or identify further associations. As no studies investigating polygenic risk with clinical symptoms and/or self-reported personality and mood could be found, these are areas which may prove to be highly beneficial.

Future such studies could also benefit from the creation of a cross-disorder polygenic risk profile score in view of the evidence for a shared genetic aetiology for major psychiatric disorders.

A recent imaging study by Whalley et al., (2014) reported an impact of cumulative genetic risk using a cross-disorder risk profile score generated from the shared genetic effects of five major mental illnesses and this approach may also prove to be informative from a neuropsychological perspective.

6.8 Conclusions

This first full neuropsychological assessment of the unique *DISC1 t*(1;11) kindred has provided evidence that *DISC1* impacts upon general intelligence and attention and processing speed, supporting earlier work by Blackwood et al., (2001). Premorbid to current IQ difference is significantly reduced in carriers and current IQ is also particularly impaired in individuals who have both the *t*(1;11) translocation and psychotic disorder, suggesting that *DISC1* may increase the risk for major psychiatric disorder through an impact on general intelligence and further, those who carry the rare genetic risk factor (*DISC1 t*(1;11) balanced translocation) may be subject to a 'double hit' as the development of a psychotic disorder would likely result in a further insult on intelligence. Overall these results support the role of *DISC1* as a risk factor for the development of major psychiatric disorders, in particular schizophrenia, bipolar disorder and major depressive disorder.

Polygenic risk for major depressive disorder was found to be significantly associated with impaired general intelligence (current IQ) and slowed reaction time in patients who were not currently depressed suggesting there may be genetic risk markers in this population which impact on cognition. This is a novel finding and further suggests the possibility of a biological component related to the genetics of depression.

This is the first full investigation of the *DISC1 t*(1;11) translocation and also one of the first studies to relate polygenic risk profile scores to measures of cognition. Results confirm the importance of *DISC1* for increasing risk of major mental illness and identify promising new areas for future research with regard to polygenic risk for major depressive disorder and cognition which may aid understanding and help to identify and create new treatment targets to improve outcomes for those living with major mental illness.

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Appendices

Appendix 1

Genotyping

Genotypes of common nonsynonymous variants in DISC1 were extracted from whole genome sequencing data. Whole genome sequencing was performed by W. Richard McCombie at The Stanley Institute for Cognitive Genomics, Cold Spring Harbor Genomics Centre under an NIH grant awarded to W. Richard McCombie and David J. Porteous (CGE, IGMM, University of Edinburgh; NIH award R01MH102088).

Briefly, whole genome sequencing of whole blood-derived DNA, or lymphoblastoid cell line-derived DNA, was performed on an Illumina HiSeq 2000 at an average read depth of >30x. Sequence reads from the Illumina HiSeq 2000 runs were aligned to human genome assembly hg19 using the BWA aligner [1], allowing 2 mismatches in the 30-base seed. Alignments were then paired, imported to binary (bam) format, sorted and indexed using SAMtools[1]. Picard was then used to fix any mate pair information altered by the sorting. Bamtools[2] was used to filter alignments to retain only properly paired reads (reads aligned with appropriate insert size and orientation). PCR duplicates were removed using Picard. Bamtools[2] was then used to select alignments with a minimum mapping quality score of 20. Target coverage for each NimbleGen exome capture was assessed using Picard's HSmetrics utility, and both depth and breadth of coverage were reviewed for each sample. The Genome Analysis Toolkit[3] GATK was used for local read realignment around indels, and for base quality score recalibration using corrections for base position within the Illumina read, for sequence context, and for platform-reported quality. Variants were filtered for a minimum confidence score of 30, and minimum mapping quality of 40.

Additional filters were applied for base quality score, strand bias and homopolymer stretches. SNP clusters (>3 SNPs per 10 bp window) were excluded. SNPs falling within called indel regions were also masked.

Genotypes were checked using Merlin[4] to identify errors in Mendelian segregation. Pedigree relationships were verified between samples by calculation of identity by state matrices between all individuals using a linkage disequilibrium pruned dataset of >100,000 variants in PLINK[5].

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Appendix 2

Polygenic Profile Scores

Polygenic profiles scores were generated from the whole genome sequencing data using the latest Psychiatric Genomics Consortium summary GWAS reference data (SCZ2[1], BP2[2], MDD1[3]) following Purcell *et al*. 2009[4], with the following adjustments. Polygenic profiling was performed using PLINK, and as scoring was performed on a single family, no pruning for linkage disequilibrium was performed. This is unlikely to have a major effect (see Purcell *et al*., 2009[4] Supplementary Information). As recommended by Dudbridge (2013), no p-value threshold was applied to the summary data, maximising the information retained. Scores were standardise with a mean of 0 and a standard deviation of 1. Higher positive scores represent a higher polygenic risk of psychiatric illness. The number of variants scored in each individual was retained and used as a covariate in all analyses.

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